Single Technology Appraisal

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Contents:

The following documents are made available to stakeholders:

1. **Response to the Draft Guidance Document 2 (DG2) from Pfizer**:
   a. Response form
   b. Additional evidence addendum

2. **Consultee and commentator comments on the Draft Guidance 2 Document** from:
   a. AOFAC Foundation
   b. National Haemoglobinopathy Panel
   c. UK Forum on Haemoglobin Disorders
   d. Sickle Cell Society

3. **Comments on the Draft Guidance 2 Document received through the NICE website**

4. **External Assessment Group critique of company response to draft guidance 2** prepared by Liverpool Reviews and Implementation Group (LRiG)

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Pfizer UK Ltd.
• Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nothing to disclose.
Name of commentator person completing form:	[redacted]

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Executive summary** The company would like to thank the NICE committee for issuing an updated draft guidance and explicitly expressing their preferred scenario for cost-effectiveness. The company appreciates the steps the committee has made to recognise the historic and ongoing inequalities relating to people with sickle cell disease (SCD), particularly the systemic underfunding of research into SCD. As a result, there is an increased necessity for expert clinical opinion when developing an accurate economic evaluation for treating haemolytic anaemia in people with SCD. The company welcome the committee's decision to align with the company base case for their preferred assumptions relating to, utility benefit, haemoglobin increase after transfusion, time-to-event analysis and the rate of transfusion therapy in the standard of care (SOC) arm. In response to the ACD, the company has attempted to address the following outstanding uncertainties: • Positioning: Providing further comments on the uncertainties highlighted in the draft guidance around second line positioning of voxelotor • Regular transfusion therapy with voxelotor: a new observational study (Retrospective Real World Oxbryta Data Collection and Analysis Study [RETRO]) which provides real-world evidence (RWE) demonstrating the impact of voxelotor reducing the rate of regular transfusion therapy (RTT) by [redacted]%. This estimate is also supported by additional evidence from the Symphony Database, a small UK RWE study and three other single centre/case study reports. The result from the RETRO study has been applied in the updated company base-case and informed scenario analyses. • Long-term outcomes related to VOCs and ad hoc transfusions: Post hoc analyses from the HOPE-open label extension (OLE) study identified a statistically significant reduction in the mean number of VOCs per patient per year (PPPY) in the continuing voxelotor group compared with the voxelotor naïve group. This estimate has been explored in scenario analysis to demonstrate the impact of this uncaptured benefit. The HOPE-OLE also demonstrated a reduction in the number of ad hoc transfusions PPPY. The impact in reducing the need for ad hoc transfusions is not captured within the model, however it would likely improve the cost-effectiveness results. In addition to the new evidence and updated base-case, the company has proposed an increased PAS of [redacted]%, corresponding to a net price of £[redacted] per pack representing an additional [redacted]% discount versus the previous PAS submitted. This results in an updated company base-case ICER of £[redacted]/QALY. The company has tried to represent a complex disease most accurately with the evidence available, and where possible conducting de novo research to fill evidence

Please return to: **NICE DOCS**

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

	gaps. We acknowledge the uncertainties still present in the evidence base and possible decision error associated with this complicated disease area. However, we believe that the updated commercial offer and the new ICER range presented based on the latest available evidence, results in a significant improvement in the cost-effectiveness results and represents value for money for the NHS.
2	**Section 3.3 Population** The company welcomes the committee's decision to appraise voxelotor in line with the company's second line positioning, however, noting that there is still some level of uncertainty remains. In order to address this uncertainty, the company would like to clarify that whilst the terminology second line is not exact and is open for interpretation in the context of SCD, the position has been widely supported by clinical experts. There is an international consensus that all patients with SCD should be offered hydroxycarbamide; this is reflected in numerous guidelines including the British Society of Haematology who recommend hydroxycarbamide for all patients with SCD prior to any other treatment. In addition, hydroxycarbamide is licenced in the UK in SCD patients over 2 years of age 10 whereas voxelotor is indicated in those 12 years and above. It is therefore highly likely that SCD patients presenting with symptoms of the disease in childhood would be offered hydroxycarbamide first since there is no other alternative licenced medicine available. Hydroxycarbamide was available in all countries in the HOPE trial. Two thirds of patients in the HOPE trial were receiving hydroxycarbamide, and it is reasonable to assume that the decision to enrol onto the trial was made because current management of their SCD was not optimal (i.e. an insufficient response to hydroxycarbamide). It is important to note that a stable dose does not equate to stable disease, some patients reach the maximum permitted dose of hydroxycarbamide and lose effectiveness. Due to the availability of hydroxycarbamide and its recommendation in treatment guidelines, it is likely that for patients in HOPE who were not taking hydroxycarbamide, it had been either considered and was not suitable or had been used in the past (i.e. patients were ineligible, intolerant, or hydroxycarbamide was insufficiently effective), as it is common practice to only enrol patients who have no licenced alternatives. As noted in paragraph 177 of the Appeal Decision, clinical experts said the proposed position was appropriate in reflecting likely clinical practice.[1] With regards to the suitability of the HOPE trial, the clinical experts also noted that hydroxycarbamide is the standard first-line treatment in NHS practice, and indeed, the high proportion of patients receiving hydroxycarbamide in the HOPE trial was itself an indication that this was not a low risk population. They felt that patients would not have taken part in a trial if their disease had been adequately controlled, and the trial included patients who would otherwise have been eligible for RTT[1]. For these reasons, the company believe the HOPE trial is representative of patients who will use voxelotor in the NHS, of these a proportion will likely receive treatment with RTT to manage their disease in the absence of any alternatives (reflected in the treatment disposition of SOC). The uncertainties around the rate of RTT will be discussed in comment 3.

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

	Additionally, as the second draft guidance states, in the model there is a higher proportion of patients on voxelotor monotherapy than observed in the HOPE trial; however, treatment efficacy results have been adjusted to reflect this. It is worth noting that voxelotor demonstrated improvements in haemoglobin response across all subgroups in the HOPE clinical trial, regardless of baseline haemoglobin, hydroxycarbamide use, VOC history, age, sex or race.[2] Furthermore, a new observational study [RETRO, (NCT04930328)] provides further evidence on the real-world use of voxelotor. Please see details and results of the study under comment 3 and in Appendix A.
3	**Section 3.11 Regular transfusion therapy (RTT) with voxelotor** The company accepts that similar patient populations need to be compared between SOC and voxelotor in the model and that the committee's preferred base case assumes [redacted]% of patients would be on RTT on both arms. However, the company do not believe that the proportion of patients on RTT in the voxelotor arm would remain at this level once voxelotor treatment is initiated. In addition to the evidence provided during the previous appraisal, this assumption is now further supported by: • the latest evidence from a new observational study (RETRO), • the updated post-hoc analysis from HOPE open label extension (OLE), • and real-world evidence (RWE) from the UK and single-centre and case studies. In order to receive further confirmation from clinicians on this assumption, Pfizer also conducted a digital advisory board (conducted between 11-18th March, 2024), specifically focusing on the assumptions around the rate of RTT with or without voxelotor. **Retrospective Real World Oxbryta Data Collection and Analysis Study (RETRO, NCT04930328)** RETRO is a post marketing, multicentre, retrospective study of patients ≥ 12 years diagnosed with SCD treated with voxelotor, conducted across nine clinical sites in the US. The results showed a reduction in red blood cell (RBC) transfusions after patients started treatment with voxelotor. Transfusion data was analysed from [redacted] patients, the transfusion rate per-patient-per-year (PPPY) prior to starting voxelotor was [redacted] (SD, [redacted]) compared to [redacted] (SD, [redacted]) in the 1 year following. A subgroup analysis of patients with ≥ 6 transfusions (aligned to the definition of RTT in the model; n = [redacted]), showed that the transfusion rate PPPY decreased from [redacted] (SD, [redacted]) in the year before voxelotor to [redacted] (SD, [redacted]) in the year following. This equates to a reduction of [redacted]% (SD, [redacted]). For more detailed results, please see Addendum. This aligns with the findings of a retrospective analysis of patients ≥ 12 years diagnosed with SCD from the **Symphony Database (Shah et al**.[3]), referenced in B.2.6.9 of the original company submission. Of patients with ≥1 transfusion in the 3 months prior to starting voxelotor (n = 190), the mean annualised transfusion rate decreased from 7.0 (95% CI, 6.4–7.5) to 3.3 (95% CI,2.6–4.1) (-52%,P < 0.001).[3] The RETRO analysis has a couple of key advantages compared with the Symphony database analysis conducted b Shah et al.[3] Firstly, the pre- and post-voxelotor treatment period is longer (12 months vs 3 months) thus helping to reduce the potential regression to the mean effect. The RETRO data is of higher quality because it used a

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

	standard electronic data capture (EDC) form similar to clinical trials at all sites. Sites were trained on the data capture. The data also underwent Level 1 and 2 cleaning, which meant any errant data entry or certain missing data was tracked down by data quality.[4] **UK real world evidence (Sanius Health)** Another study monitoring the real-world impacts of voxelotor treatment on RBC transfusion requirements in [redacted] UK patients with SCD who received voxelotor for nearly 18 months (mean ± SD of 526 ± 178 days) found that prior to voxelotor treatment, [redacted] patients had required a RBC transfusion, of which [redacted] required regular transfusions (every < 6 weeks). Following voxelotor initiation, only [redacted] patient required any form of transfusion.[5] **Single centre and case studies** The evidence from these studies, is supplemented by a number of single centre and case studies, reporting the experiences of 24 patients treated with voxelotor, in the US and Qatar (a single case study).[6-9] One study including seven patients reported transfusions decreased by 60% in the 24 weeks following voxelotor initiation.[9] Another reported among the 13 patients treated with voxelotor nine required fewer RBC units, falling from 16.6 RBC units in the prior to treatment with voxelotor to 9.6 RBC units in the year during treatment.[7] A third concluded in patients with SCD who receive frequent simple or exchange blood transfusions for indications other than stroke prevention, tapering the amount of blood administered is possible, and should be considered when these patients are treated with voxelotor.[8] **Clinical Expert advice** The assumption that the rate of RTT with voxelotor is equal to the rate with SOC does not reflect the advice provided by the clinical experts consulted by NICE during and beyond the appraisal committee meetings, who stated in their comments on the draft guidance document *"…most clinicians would not use voxelotor and chronic transfusion as a combination therapy. Voxelotor would be used as an alternative to chronic transfusion"*.[10] Based on this, since voxelotor would be used as an alternative to chronic transfusion and combination therapy is unlikely, it is reasonable to expect fewer RTT in the voxelotor arm of the model. Equally, in the SOC arm, where voxelotor is not available, a proportion of these patients would have to be treated with regular transfusions in the absence of any alternative treatments, resulting in a higher number of regular transfusions in the SOC arm. This is also supported by The American Society of Hematology Guideline Monitoring Expert Working Group who noted that voxelotor, should be considered to improve the baseline haemoglobin in certain patients to minimise future RBC transfusions[11], effectively naming voxelotor as an alternative to regular transfusions. In order to gather further insights from clinicians on this assumption, Pfizer conducted an advisory board involving [redacted] haematologists who represent the most key treatment centres for SCD, [redacted] haemoglobinopathy coordinating centres (HCC) within England. In this advisory board we asked a poll question; with the routine availability of voxelotor, what impact they believed voxelotor may have on RTT in patients with SCD. There were [redacted] responses: [redacted] ([redacted]) believed that voxelotor will decrease RTT in patients with SCD, [redacted]% ([redacted]) believe that voxelotor will have no change on RTT amongst patients with SCD. [redacted] haematologist did not respond.[12] **Conclusion**

Please return to: **NICE DOCS**

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

	Based on clinical expert opinion, multiple studies, and published single centre and case studies, the committee's preferred assumption of equal transfusion rates in both treatment arms persisting over the time horizon of the model (lifetime horizon), with equal rates of RTT discontinuation (5% per year) does not reflect clinical practice. In addition, the long-term randomised clinical trial evidence from HOPE-OLE supports that treatment with voxelotor reduces the need for transfusions over time. Please see detailed results under comment 4. Whilst it is difficult to separate regular transfusions from ad hoc RBC transfusions in the literature, the evidence shows that overall transfusion burden reduces with voxelotor and transfusion rates decline more significantly in the subgroup of patients with the highest number of transfusions. Therefore, the committee's current assumption is incorrect, overly conservative and not supported by evidence that RTT rate is similar in both arms. **Updated base-case** Based on the new evidence, we believe there is a clear rationale to support a modified approach to the Committee's preferred assumption of identical rates of RTT in SOC and voxelotor. RETRO has demonstrated that in the year prior to voxelotor initiation, RTT patients had on average [redacted] transfusions per year, which is similar to our model where RTT costings assume [redacted] transfusions per year. However, in the year following voxelotor initiation, RETRO demonstrated that the number of transfusions in this group was reduced by [redacted]%. For simplicity, we have applied this relative reduction in the model by reducing the percentage of patients on RTT in the voxelotor arm to [redacted]% [redacted] from day one. We have explored the impact of this assumption in scenario analysis.
4	**Section 3.7 Long term complications** The company are pleased that the committee have considered that, as a rare disease with limited evidence available, the level of evidence supporting surrogate endpoints is not as high as in other conditions and is therefore willing to apply more flexibility when estimating the impact of voxelotor on long-term SCD related complications. The committee however note the high levels of uncertainty in this assumption. The company have shared new post-hoc analysis from the HOPE-OLE which supports this assumption. **VOCs**: The HOPE trial was not powered or designed to show differences in VOCs; nearly half (42%) of patients had only one VOC in the year before enrolment, and those with > 10 were excluded. Nonetheless, the proportion of patients who experienced a VOC event during the study was numerically lower in the voxelotor 1500 mg group compared to the placebo group (69.3% vs 76.9%). The total number of VOC events was also numerically lower in the voxelotor than in the placebo group (219 vs 293); however, differences were not statistically significant.[2] Post-hoc analysis of the HOPE-OLE data was collected on the number VOCs from the start of the OLE through 28 days after voxelotor discontinuation, similar to RBC transfusions. VOCs were events reported as SCD with crisis or acute chest syndrome. These results demonstrated a reduction in VOCs. A statistically significant reduction of [redacted]% was observed in the mean number of VOCs per patient per year (PPPY in the

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

	continuing voxelotor group ([redacted] [SD, [redacted]] vs [redacted] [SD, [redacted]], [redacted]) compared with the voxelotor naïve group. This reduction in VOC events, supports the assumption of long-term benefit associated with continued improvement in haemoglobin levels caused by voxelotor, acting on the underlying molecular basis of SCD. **Ad hoc transfusions:** The HOPE trial did not show a decrease in ad hoc transfusions, however further data on transfusion therapy has been collected from participants in the HOPE open label extension (OLE) for the period from the start of the OLE. Patients who completed the phase 3 HOPE trial (i.e. completed 72 weeks of treatment) were eligible to enrol in the multicentre HOPE Open Label Extension (OLE) study (n = 199). Participants randomised to the placebo (n =62 [34.8%]) or the voxelotor 900 mg arms (n = 58 [32.5%]) of the HOPE trial started once daily voxelotor 1500 mg upon entering the OLE; participants randomised to the 1500 mg arm (n = 58 [32.5%]) of the HOPE trial continued at this dose if they derived clinical benefit and/or until voxelotor was available via an alternative source (commercialisation or a managed access program). Data were collected on the number of RBC transfusions from the start of OLE through 28 days after voxelotor discontinuation. The mean duration of exposure to voxelotor in the OLE was [redacted] years for those previously treated with placebo in HOPE (voxelotor naïve) and [redacted] years for those continuing voxelotor. The total exposure to voxelotor was [redacted] years for patients continuing on voxelotor 1500mg. The analysis demonstrated a reduction in RBC transfusions. The mean number of transfusions PPPY was lower in the continuing voxelotor group ([redacted] [SD, [redacted]] vs [redacted] [SD, [redacted]], p=[redacted]) compared with the voxelotor naïve group, with the mean number of transfusions per patient [redacted]% lower in the group continuing voxelotor [redacted] vs [redacted]). The results were not statistically significant. For more detailed results, please see Addendum. The reduction in the need for RBC transfusions supports the long-term benefit associated with continued improvement in haemoglobin levels caused by voxelotor. Whilst patients receiving regular scheduled transfusions were excluded from HOPE there was no limit on the number of ad-hoc RBC transfusions that can be given. Ad hoc transfusions still present a considerable burden to the healthcare system; this phase 3 randomised controlled trial evidence demonstrates the long-term reduction in transfusions in patients treated with voxelotor. It is important to note that the impact in reducing the need for ad hoc transfusions is not captured within the model, which would likely improve the cost-effectiveness results.

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

5	**Company's updated base case** The latest results from the RETRO and HOPE-OLE studies have been incorporated in the updated company model and tested in scenario and sensitivity analyses. The updated company base case includes the following changes to the model: • The rate of RTT in the voxelotor arm is calculated based on RETRO observational study by applying the relative reduction of [redacted]% to the SOC arm, to reflect the results observed in the subgroup of patients with 6 or more RBC transfusion prior to voxelotor. Therefore, RTT on the voxelotor arm equals to [redacted]%. • Reduced net price of £[redacted] per pack. This resulted in a new company base case ICER of £[redacted]/QALY, which is within the range that NICE considers an acceptable use of NHS resources. The following assumptions were tested in scenario analyses: • Applying the data from the HOPE-OLE trial on the reduction on VOCs with voxelotor. In order to do this, the model was updated to remove the previous time-to-event equation for incidence of VOCs; in its place a constant incidence rate of [redacted] VOCs per year for voxelotor and [redacted] VOCs per year for SoC was used in an exponential time-to-event equation with no covariates. • The rate of RTT in the voxelotor arm was calculated based on RETRO observational study by assuming a delayed treatment effect. In order to apply this scenario, rates of RTT on both arms starts with [redacted]% of patients receiving RTT and the relative reduction in RTT of [redacted]% was applied after 1 year on the voxelotor arm. A switch was programmed into the model such that at the end of year one [redacted]% of patients have discontinued RTT on a one-off basis. The company considers this scenario to be overly conservative and not in line with clinical evidence as the RETRO data and other evidence shows immediate treatment effect in the 1st year after introduction of voxelotor. The company considers the new base case to be conservative as there are significant benefits that are not captured in this scenario. For simplicity, VOC incidence rates from HOPE-OLE were not incorporated in the new base case; however they represent a significant uncaptured benefit. Another area of uncaptured benefit is the reduction in ad-hoc transfusions from the HOPE-OLE trial, which is not captured in the cost-effectiveness results as it would have required significant changes to the model, which was not feasible during the timeframe of this consultation. Further details of the preferred base case, scenario analyses and granular cost-effectiveness outcomes are provided in Addendum.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

Table 1. Summary of model changes

Model change	Description	Assumption	ICER (cost/QALY)
-	Committee's preferred assumptions	-	[redacted]
New price	Committee's preferred assumptions + new PAS		[redacted]
Company's new base case	Rate of RTT in the voxelotor arm based on RETRO observational study. Relative reduction of RTT by [redacted]% at baseline	RTT in voxelotor baseline: [redacted]%	[redacted]
Scenario 1	Hypothetical scenario to test the sensitivity of the ICER to different assumptions around RTT displacement with voxelotor. Rate of RTT in the voxelotor arm based on RETRO observational study, assuming a delayed treatment effect; with both arms starting with [redacted]% of patients receiving RTT and applying the relative reduction in RTT of [redacted]% after 1 year.	RTT in voxelotor baseline: [redacted]% RTT in voxelotor year 1: rate of discontinuation [redacted]% RTT in voxelotor year 2+: rate of discontinuation default (5%)	[redacted]
Scenario 2	New base case + VOC incidence using results from the HOPE-OLE trial	RTT in voxelotor baseline: [redacted]% Constant VOC incidence rate: Voxelotor: [redacted] per year SOC: [redacted] per year	[redacted]
Scenario 3	Scenario 1 + time-to-event equations populated with the VOC incidence from HOPE-OLE	RTT in voxelotor baseline: [redacted]% RTT in voxelotor year 1: rate of discontinuation [redacted]%	[redacted]

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

			RTT in voxelotor year 2+: rate of discontinuation default (5%)	
			Constant VOC incidence rate: Voxelotor: [redacted] per year SOC: [redacted] per year	
	Scenario 4	Hypothetical scenario to test the sensitivity of the ICER on different assumptions around RTT displacement with voxelotor. Testing the sensitivity of the ICER on continued reduction in RTT beyond 1 year after initiation of voxelotor.	Baseline: [redacted]% Year 1: rate of discontinuation [redacted]% Year 2: rate of discontinuation [redacted]% Year 3+: rate of discontinuation default (5%)	[redacted]
	OLE: open-label extension; RTT: regular transfusion therapy; SOC: standard of care; VOC: vaso-occlusive crisis			

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is [redacted] and information that is [redacted]. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

References

1. National Institute for Health and Clinical Excellence. Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403] Appeal. 2023. Available from: https://www.nice.org.uk/guidance/gid-ta10505/documents/html-content-11.
2. European Medicines Agency. Oxbryta: EPAR - Public Assessment Report. 2022. Available from: https://www.ema.europa.eu/en/documents/assessment-report/oxbryta-epar-public-assessment-report_en.pdf [accessed March 2022].
3. Shah N, Lipato T, Alvarez O, et al. Real-world effectiveness of voxelotor for treating sickle cell disease in the US: a large claims data analysis. Expert Review of Hematology. 2022;15(2):167-73.
4. Pfizer. A Retrospective Data Collective and Analysis Study of Patients with Sickle Cell Disease (SCD) Who Have Been Treated With Oxbryta (Voxelotor) - Protocol. 2021.
5. Sanius Health. Monitoring the Real-World Impacts of Voxelotor Treatment on Blood Transfusion Requirements, Quality of Life, and Physiological Wearable Metrics in UK Patients with Sickle Cell Disease. (Pfizer Data on File). 2023.
6. Alshurafa A, Yassin MA. Case report: Safety and efficacy of voxelotor in a patient with sickle cell disease and stage IV chronic kidney disease. Frontiers in Medicine. 2022;9.
7. Bade NA, Giri U, Wang H, Ershler WB. Reduced red cell transfusions and hospitalizations in sickle cell patients treated with voxelotor—Experience from a single center. Transfusion. 2022;62(7):1462-4.
8. Baruwa Etti A, Jones S, Andemariam B. 5610357: Reduction in Blood Transfusion Burden Following Initiation of Voxelotor or Crizanlizumab: A Case Series. HemaSphere. 2023;7(S1).
9. Blyden G, Bridges KR, Bronte L. Case series of patients with severe sickle cell disease treated with voxelotor (GBT440) by compassionate access. American Journal of Hematology. 2018;93(8):E188-E90.
10. National Institute for Health and Clinical Excellence. Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403] Committee Papers. 2023. Available from: https://www.nice.org.uk/guidance/gid-ta10505/documents/committee-papers-2.
11. Chou ST, Hendrickson JE, Fasano RM. Transfusion therapy for sickle cell disease: what's new? Blood Advances. 2023;7(11):2551-3.
12. Pfizer. Asynchronous digital advisory board. Data on file. 2024.

Please return to: **NICE DOCS**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Voxelotor for treating haemolytic anaemia in people with sickle cell disease [ID1403]

Draft Guidance 2: Addendum A

March 2024

File name	Version	Contains confidential information	Date
ID 1403 Draft guidance addendum	**V1**	**Yes**	**2024.03.19**

Contents

Tables and figures

Tables

Figures

1 Introduction

This document provides updated evidence supporting the submission for voxelotor for treating haemolytic anaemia in people with sickle cell disease (SCD), which was submitted to NICE in June 2022. In response to uncertainties raised in the 2024 draft guidance document, the company have provided further evidence generation to address these uncertainties in the cost-effectiveness model (CEM). The additional evidence and updates to the CEM are described in this addendum, for consideration by NICE ahead of the fourth Appraisal Committee meeting (ACM).

In brief, additional evidence from RETRO observational study has been incorporated into the CEM to reduce the uncertainties around the proportion of patients who receive regular transfusion therapy (RTT) in the voxelotor arm (Section 2.1.1). New post-hoc analysis from the HOPE open-label extension (OLE) are also presented and incorporated in the CEM, as part of scenario analysis, modelling the impact of voxelotor on long-term SCD related complications through the reduction of vaso-occlusive crises (VOCs; Section 2.1.2).

In addition, to reflect the remaining uncertainties around RTT rates in patients treated with voxelotor, [redacted] (Section 2.1.3).

An updated version of the CEM is supplied alongside this document. Updated results for the company post draft guidance base case and sensitivity analyses following incorporation of the new evidence outlined above are summarised in Section 2.2. These results supersede those supplied in the company response to the second ACM and are referred to as the ‘base case’ hereafter. In summary, the new base case ICER with [redacted] is [redacted].

The company considers the new base case to be conservative as there are significant benefits that are not captured in this scenario.

2 Summary of changes to cost-effectiveness

Table 1 presents the summary of the changes to the company's cost-effectiveness model.

Table 1. Summary of changes to cost-effectiveness outcomes when applying changes to model assumptions

Model change	Description	Scenario	ICER (cost/QALY)
-	Committee's preferred assumptions	-	[redacted]
	Committee's preferred assumptions with new PAS		[redacted]
Company's new base case	**Rate of RTT in the voxelotor arm based on RETRO observational study relative reduction of RTT by [redacted]% at baseline**	**RTT in vox baseline: [redacted]%**	[redacted]
Scenario 1	Rate of RTT in the voxelotor arm based on RETRO observational study, with both arms starting with [redacted]% of patients receiving RTT and applying the relative reduction in RTT of [redacted]% after 1 year	RTT in vox baseline: [redacted]% RTT in vox year 1: rate of discontinuation [redacted]% RTT in vox year 2+: rate of discontinuation default (5%)	[redacted]
Scenario 2	Scenario 1 + VOC incidence using results from the HOPE-OLE trial	RTT in vox baseline: [redacted]%	[redacted]
		Constant VOC incidence rate: Voxelotor: [redacted] per year SOC: [redacted] per year	
Scenario 3	New base case + VOC incidence using results from the HOPE-OLE trial	RTT in vox baseline: [redacted]% RTT in vox year 1: rate of discontinuation [redacted]% RTT in vox year 2+: rate of discontinuation default (5%)	[redacted]
		Constant VOC incidence rate: Voxelotor: [redacted] per year SOC: [redacted] per year	
Scenario 4	Hypothetical assumption to test the sensitivity of the ICER. Testing the sensitivity of the ICER on continued reduction in RTT over time after initiation of voxelotor	Baseline: [redacted]% Year 1-2: rate of discontinuation [redacted]% Year 3+: rate of discontinuation default (5%)	Dominant[redacted]

OLE: open-label extension; RTT: regular transfusion therapy; SOC: standard of care; VOC: vaso-occlusive crisis

2.1. New evidence to inform revised cost-effectiveness results

The following section outlines the new evidence presented which informed the changes to the company preferred base case model based on feedback received from NICE/EAG in the second draft guidance.

2.1.1. RETRO study - use of regular transfusion therapy

2.1.1.1. *Study design and results*

The committee were concerned with the evidence supporting reduced RTT rates for patient's treated with voxelotor and preferred that the rate of RTT in the voxelotor arm of the CEM should be equal to the rate of RTT in the standard of care (SOC) arm.

To address this uncertainty, the company have provided new supportive evidence for the reduction in RTT following treatment with voxelotor in the Retrospective Real World Oxbryta Data Collection and Analysis Study (RETRO, NCT04930328). RETRO is a multicentre, retrospective, observational study conducted at nine clinical sites in the US. The study aimed to collect and analyse retrospective data on voxelotor in the real-world setting, including data on the occurrence and number of red blood cell (RBC) transfusions following treatment with voxelotor. Eligible patients were aged ≥ 12 years, were diagnosed with SCD, had been receiving voxelotor for ≥ 2 consecutive weeks, and had laboratory and clinical data available from one year before and up to one year after their first voxelotor dose. RBC transfusions were compared before and after voxelotor exposure using the incidence rate per-patient-per-year (PPPY) and the mean percentage change in number of RBC transfusions per patient. The reasons for transfusion, and the number of units transfused, were not captured.[1]

Primary outcomes from the RETRO study were presented at the 2023 European Hematology Association congress by Andemariam et al.[2]

Table 2 Demographics and baseline characteristics of patients in the RETRO study

Characteristic	Patients (N = 216)[a]
Age, years	
Mean (SD)	33.7 (14.3)
Range	12.1-71.0
Age, group, n (%)	
< 18 Years	31 (14.4)
18 to <45 years	136 (63.0)
45 to <65 years	42 (19.4)
≥65 years	7 (3.2)
Sex, n(%)	
Male	96 (44.4)
Female	120 (55.6)
Race or ethnic origin, n (%)	
Black or African American	189 (87.5)
White	5 (2.3)
Other	22 (10.2)
Sickle cell genotype	
HbSS	199 (92.1)
HbSβ^0	10 (4.6)
Other[b]	22 (10.2)
Baseline Haemoglobin (g/dL)	
Mean (SD)	7.8 (1.5)
Range	4.3 – 13.5
Baseline Haemoglobin group	
<7 g/dL	62 (28.7)
7-10.5 g/dL	141 (65.3)
>10.5 g/dL	9 (4.2)
HC at baseline, n (%)	
Yes	134 (62.0)
No	81 (37.5)

[a] Data missing for SCD genotype (n = 1), baseline Hb (n = 4), and HU use at baseline (n = 1).
[b] Includes HbSβ+ (n = 3), HbSC (n = 2), and HbS/O-Arab (n = 1).
HbSβ^0: Haemoglobin Sβ^0; HbSS: homozygous haemoglobin S; HC: Hydroxycarbamide; SD: standard deviation

The results of the study showed a reduction in RBC transfusions after patients initiate voxelotor treatment. Transfusion data was analysed from [redacted] patients, the transfusion rate per-patient-per-year (PPPY) prior to starting voxelotor was [redacted] (SD, [redacted]) compared to [redacted](SD,[redacted]) in the 1 year following. This equates to a [redacted]% reduction in transfusion rate PPPY. Of patients with ≥ 2 transfusions in the year prior to initiating voxelotor the difference was even more significant, [redacted]%. A subgroup analysis of patients with ≥ 6 transfusions (aligned to the definition of RTT in the model) in the year prior to initiating voxelotor (n = [redacted]), showed that the transfusion rate PPPY reduced by [redacted]% (SD, [redacted]) after treatment with voxelotor for 1 year; PPPY transfusion rates decreased from [redacted] (SD, [redacted]) in the year before voxelotor to

[redacted] (SD, [redacted]) in the year following (Table 3). These subgroup results have been used in the company's updated base case to inform rates of regular transfusion rate on the voxelotor arm.

Table 3. Results of RETRO subgroup analysis exploring patients with ≥6 prior RBC transfusions

	Overall population (n=[redacted])		≥2 prior RBC Transfusions (n=[redacted])		≥6 prior RBC Transfusion (n=[redacted])	
Measure	Before vox	After vox	Before vox	After vox	Before vox	After vox
RBC Transfusion Count	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RBC Transfusion Rate per-person-per-year (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean absolute change in RBC transfusion rate (SD)	[redacted]		[redacted]		[redacted]	
Mean percentage change in per-person RBC transfusions (SD)	[redacted]		[redacted]		[redacted]	
SD: standard deviation; RBC: red blood cell; vox: voxelotor						

2.1.1.2. *Incorporation of RETRO data into the cost-effectiveness model*

This new evidence supporting the reduction of RTT rates over time in patients treated with voxelotor has been incorporated into the CEM. In the company's new base case, the rate of RTT use on the voxelotor arm was calculated by applying the relative reduction of [redacted]% to the SOC arm [redacted], to reflect the results observed in the subgroup of patients with 6 or more RBC transfusion prior to voxelotor in RETRO. The rate of RTT in the voxelotor arm at baseline in the company's new base case is [redacted]%.

Results of this change to the CEM base case are reported in Section 2.2.

2.1.2. HOPE OLE – VOC incidence and use of regular transfusion therapy

New evidence showing the impact of voxelotor on the incidence of VOC in the HOPE-OLE. This evidence was incorporated into the model for the purpose of scenario analyses but was not used in the new company base case assumptions.

2.1.2.1. *Study design and results*

The committee noted that the HOPE trial did not show any treatment effect relating to the requirement for rescue transfusions. However, further data on transfusion therapy has been collected from participants in the HOPE-OLE for the period from the start of the OLE. In addition, this update from the HOPE-OLE provides additional data supporting the impact of voxelotor on long-term SCD related complications through the impact on VOCs.

Patients who completed the phase 3 HOPE trial (i.e completed 72 weeks of treatment) were eligible to enrol in the multicentre HOPE-OLE (NCT03573882). Participants randomised to the placebo or the voxelotor 900 mg arms of the HOPE trial newly once daily voxelotor 1500 mg upon entering the OLE; participants randomised to the 1500 mg arm of the HOPE trial continued at this dose if they derived clinical benefit and/or until voxelotor was available via an alternative source (commercialisation or a managed access program). Data were collected on the number of RBC transfusions and VOCs from the start of OLE through 28 days after voxelotor discontinuation. RBC transfusions and VOCs that occurred during the OLE were calculated as the proportion of patients with an event, incidence rate as per patient per year (PPPY), and total events per patient. VOCs were events reported as SCD with crisis or acute chest syndrome. Available data are based on an interim data cut (Dec 31, 2022).

Of the 199 patients who completed the 72- week HOPE trial, 178 enrolled in the HOPE OLE with 62 (34.8%) previously on placebo, 58 (32.5%) previously on voxelotor 900 mg, and 58 (32.5%) remaining on voxelotor 1500 mg. Median age at enrolment was 25 years. The results reported here focuses only on the voxelotor naïve (patients previously receiving placebo) and continued 1500 mg voxelotor groups as these are the populations relevant to the NICE decision problem. 900 mg is an unlicensed dose of voxelotor.

Duration of exposure to voxelotor in the OLE was [redacted] years for those previously treated with placebo in HOPE (voxelotor naïve) and [redacted] years for those continuing voxelotor. The total exposure to voxelotor was [redacted] years for patients continuing on voxelotor 1500 mg. The analysis demonstrated a reduction in RBC transfusions. The

mean number of transfusions PPPY was lower in the continuing voxelotor group ([redacted] [SD, 1.01] vs [redacted] [SD, [redacted]]; p = [redacted]) compared with the voxelotor naïve group, with the mean number of transfusions per patient [redacted]% lower in the group continuing voxelotor ([redacted] vs [redacted]). The mean number of VOCs PPPY was [redacted]% lower in the continuing voxelotor 1500 mg group ([redacted] [SD, [redacted]] vs [redacted] [SD, [redacted]]) compared with the voxelotor naïve group (Table 4).

Table 4. Results switching from placebo or continuing on voxelotor 1500 mg: RBC transfusions and VOCs from the HOPE OLE, Dec 31, 2022 data cut

Measure	Group 1 (from placebo)		Group 2 (from vox 1500mg)	
	n/mean	%/SD	n/mean	%/SD
Total Time on Voxelotor (years)- HOPE + OLE	[redacted]	[redacted]	[redacted]	[redacted]
OLE Measures				
Total patients	[redacted]	[redacted]	[redacted]	[redacted]
Total patient-years during the OLE	[redacted]	[redacted]	[redacted]	[redacted]
OLE follow-up time (years)	[redacted]	[redacted]	[redacted]	[redacted]
RBC Transfusions in OLE				
Participants with RBC transfusion	[redacted]	[redacted]	[redacted]	[redacted]
RBC transfusions per patient per year	[redacted]	[redacted]	[redacted]	[redacted]
Total number of RBC transfusions per patient	[redacted]	[redacted]	[redacted]	[redacted]
Total number of transfusions	[redacted]	[redacted]	[redacted]	[redacted]
VOC in OLE				
Participant with VOC	[redacted]	[redacted]	[redacted]	[redacted]
VOC per patient per year	[redacted]	[redacted]	[redacted]	[redacted]
Total number of VOC events per patient	[redacted]	[redacted]	[redacted]	[redacted]
Total number of VOC events	[redacted]	[redacted]	[redacted]	[redacted]

OLE: open-label extension; RBC: red blood cell; VOC: vaso-occlusive crisis

2.1.2.2. *Incorporation of HOPE OLE VOC data into the cost-effectiveness model*

In order to capture the most up-to-date and mature data available for voxelotor, the model was updated to remove the previous time to event equation for incidence of VOCs. In its place a constant incidence rate of [redacted] VOCs per year for voxelotor and [redacted] VOCs per year for standard of care was used in an exponential time to event equation with no covariates.

Results of this change to the CEM are reported as scenario analyses in Section 2.2.3 (Table 11).

2.1.3. Voxelotor price

The company acknowledges the remaining uncertainty surrounding RTT rates with voxelotor in clinical practice and has submitted a revised PAS of [redacted]%, with a new net price of £[redacted]. Compared to the previous [redacted]% PAS, this is an additional [redacted]% discount, on the previous net price of £[redacted].

The updated net prices with the revised PAS are included in Table 5 below.

Table 5. Updated net prices with revised PAS

Strength	Form	Pack size	List price	Discount	Net price with PAS
500 mg	Tablet	90	£5,917.81	[redacted]	[redacted]

2.2. Revised cost-effectiveness model results

2.2.1. Preferred base-case results

2.2.1.1. *Base-case incremental cost-effectiveness analysis results*

The company's updated base case reflects the results of the RETRO observational study, where the number of transfusions in the group with 6 or more transfusion prior to starting voxelotor was reduced by [redacted]% after treatment with voxelotor for 1 year. This relative reduction was applied in the model by reducing the percentage of patients on RTT on the voxelotor arm to [redacted]% [redacted] from day one.

In the model base case, considering a lifetime horizon, the total undiscounted life years (LYs) were [redacted] for voxelotor and [redacted] for SOC; total discounted LYs were [redacted] and [redacted], respectively (Table 6). Total undiscounted quality-adjusted life years (QALYs) were [redacted] for voxelotor and [redacted] for SOC; total discounted QALYs were [redacted] and [redacted], respectively, with an incremental difference of [redacted] (Table 6). Total discounted costs were £[redacted] and £[redacted] for voxelotor and SOC, respectively, resulting in a difference of £[redacted]. The ICER was £[redacted]/QALY. The resulting ICER by the number of agents in the simulation is shown in Figure 1.

Table 6. Cumulative discounted cost-utility results (£)

	Voxelotor	SOC	Difference
Total LYs (not discounted)	[redacted]	[redacted]	[redacted]
Total LYs (discounted)	[redacted]	[redacted]	[redacted]
Total QALYs (not discounted)	[redacted]	[redacted]	[redacted]
Total QALYs (discounted)	[redacted]	[redacted]	[redacted]
Caregiver QALYs (not discounted)	[redacted]	[redacted]	[redacted]
Caregiver QALYs (discounted)	[redacted]	[redacted]	[redacted]
Patient QALYs (not discounted)	[redacted]	[redacted]	[redacted]
Patient QALYs (discounted)	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	[redacted]		
Net health benefit			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Net monetary benefit			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

LY, life years; QALYs, quality-adjusted life years; SOC, standard of care; WTP, willingness to pay

[redacted]

Figure 1. ICER by number of agents in the simulation for voxelotor vs SOC

2.2.1.2. *Base-case health outcomes*

Table 7. Patients experiencing one or more complication by the end of the simulation

	Voxelotor	SOC	Relative difference
ARF	73.5%	73.9%	-0.5%
Arrythmias	46.4%	46.3%	0.2%
CKD	36.6%	36.7%	-0.3%
ESRD	9.5%	9.6%	-1.8%
Gallstones	45.9%	46.5%	-1.4%
Heart failure	25.4%	25.4%	0.0%
Leg ulcer	16.4%	16.4%	0.0%
Osteomyelitis	16.9%	17.1%	-1.6%
Osteonecrosis	43.9%	43.5%	0.9%
Pulmonary hypertension	33.8%	34.5%	-2.2%
Sepsis	49.5%	50.1%	-1.3%
Stroke	15.7%	15.6%	0.2%
VOC	97.5%	97.7%	-0.3%
ARF, acute renal failure; CKD, chronic kidney disease; ESRD, end stage renal disease; SOC, standard of care; VOC, vaso-occlusive crises			

Table 8. Incidence rate (events per person per year)

	Voxelotor	SOC	Relative Difference
ARF	0.090	0.092	-2.7%
Arrythmias	0.085	0.087	-2.2%
CKD	0.015	0.016	-2.2%
ESRD	0.004	0.004	-3.6%
Gallstones	0.019	0.020	-3.2%
Heart failure	0.011	0.011	-1.8%
Leg ulcer	0.041	0.0418	-2.9%
Osteomyelitis	0.023	0.024	-4.2%
Osteonecrosis	0.117	0.118	-0.9%
Pulmonary hypertension	0.014	0.015	-3.9%
Sepsis	0.044	0.046	-4.1%
Stroke	0.012	0.012	-1.7%
VOC	1.807	1.973	-8.4%
ARF, acute renal failure; CKD, chronic kidney disease; ESRD, end stage renal disease; SOC, standard of care; VOC, vaso-occlusive crises			

2.2.1.3. *Base-case cost outcomes*

The breakdown of the cumulative discounted treatment costs and complication management costs is shown in Table 9.

Table 9. SCD treatment and complication costs for voxelotor vs SOC (£, discounted)

	Voxelotor	SOC	Difference
SCD treatment costs	[redacted]	[redacted]	[redacted]
Voxelotor medication	[redacted]	[redacted]	[redacted]
Voxelotor administration	£57	£0	£57
Hydroxycarbamide medication	£138	£163	-£25
Hydroxycarbamide administration	£30	£35	-£5
Regular transfusions	£36,036	£68,405	-£32,370
Other medications	£6,587	£7,488	-£901
Monitoring	£509	£501	£8
Adverse event costs	£1,173	£1,359	-£186
Complication management	**£155,711**	**£163,843**	**-£8,132**
ARF	£2,123	£2,183	-£60
Arrythmias	£996	£1,010	-£14
CKD	£9,188	£9,271	-£83
ESRD	£7,978	£8,155	-£178
Gallstones	£2,181	£2,258	-£77
Heart failure	£10,539	£10,722	-£184
Leg ulcer	£5,052	£5,150	-£97
Osteomyelitis	£5,639	£5,876	-£237
Osteonecrosis	£19,710	£19,635	£76
Pulmonary hypertension	£12,916	£13,426	-£510
Sepsis	£3,005	£3,133	-£127
Stroke	£9,613	£9,627	-£14
VOC	£66,770	£73,396	-£6,626

ARF, acute renal failure; CKD, chronic kidney disease; ESRD, end stage renal disease; VOC, vaso-occlusive crises

2.2.2. Sensitivity analysis

2.2.2.1. *Probabilistic sensitivity analysis*

The probabilistic sensitivity analysis draws values for each variable from its individual uncertainty distribution. In total, 500 simulations of 1,000 patients were performed, which gives a distribution of incremental results, and consequently, an estimate of the overall uncertainty surrounding cost-effectiveness results.

Figure 2. Cost-effectiveness plane (dashed line WTP of £36,000)

At a willingness to pay (WTP) threshold of £20,000, there is a [redacted]% chance that voxelotor is cost-effective (Figure 3). At a WTP threshold of £30,000, the probability of being cost-effective is about [redacted]%.

Figure 3. Cost-effectiveness acceptability curve

2.2.2.2. *Deterministic sensitivity analysis*

The key drivers of the economic model are regular transfusion utilisation, discontinuation and cost, voxelotor discontinuation, and mean Hb change with placebo and chronic transfusions (Figure 4).

Figure 4. Deterministic sensitivity analysis tornado plot, ICER (£)

ARCET, automated red cell exchange transfusions; CT: chronic transfusion d/c, discontinuation; Hb, haemoglobin, HU, hydroxyurea (hydroxycarbamide); SOC, standard of care

2.2.3. Scenario analyses

Scenario analyses were performed exploring various inputs and combinations as described below and in Table 10.

Scenario 1

Hypothetical scenario to test the sensitivity of the ICER on different assumptions around RTT displacement with voxelotor. The model was updated to include the rate of RTT in the voxelotor arm based on RETRO observational study, assuming a delayed treatment effect; with both arms starting with [redacted]% of patients receiving RTT and applying the relative reduction in RTT of [redacted]% after 1 year. It is important to note, that the company considers this scenario to be overly conservative and not in line with clinical evidence as the RETRO data and other evidence shows immediate treatment effect in the 1st year after introduction of voxelotor.

Scenario 2

The model was updated to include the data from the HOPE-OLE trial on the reduction on VOCs with voxelotor, to the new base case (RTT in voxelotor: [redacted]% from day one). In order to do this, the model was updated to remove the previous time-to-event equation for incidence of VOCs; in its place a constant incidence rate of [redacted] VOCs per year for voxelotor and [redacted] VOCs per year for SOC was used in an exponential time-to-event equation with no covariates.

Scenario 3

In this scenario RTT use was aligned with scenario 1 (RTT at baseline in both arms: [redacted]% with [redacted]% discontinuation rate in the voxelotor arm after 1 year). The model was updated to remove time-to-event equation for incidence of VOCs, with VOC incidence rate from the HOPE OLE trial, as described in scenario 2.

Scenario 4

Hypothetical scenario to test the sensitivity of the ICER on different assumptions around RTT displacement with voxelotor. The model was updated with base line RTT use in the voxelotor arm aligned with the SOC arm ([redacted] [NICE preferred assumption]) with the reduction in transfusions observed among those with 6 or more transfusions per year in the RETRO observational study, reflecting a [redacted] decrease. This relative reduction was applied for the first two years. From year 3 the default rate of discontinuation rate of 5% was used.
Although the RETRO study and other RWE only provides data on treatment effect for 1 year, the HOPE-OLE study shows longer term benefits with voxelotor. Therefore, assuming a continued treatment effect beyond 1 year was reasonable to test in a scenario analysis.

Table 10. List of scenarios considered

Scenario	Description	ACM 3 base case	Values assumed for the scenario analysis
Scenario 1	RETRO voxelotor RTT decrease; [redacted]% relative reduction applied after 1 year	[redacted]%	Baseline: [redacted]% Year 1: rate of discontinuation [redacted]% Year 2+: rate of discontinuation default (5%)
Scenario 2	RETRO voxelotor RTT decrease; [redacted]% of patients on voxelotor and RTT at baseline + HOPE OLE VOC data		Baseline: [redacted]% Constant VOC incidence rate: Voxelotor: [redacted] per year SOC: [redacted] per year
Scenario 3	RETRO voxelotor RTT decrease; [redacted]% relative reduction applied after 1 year + HOPE OLE VOC data		Baseline: [redacted]% Year 1: rate of discontinuation [redacted]% Year 2+: rate of discontinuation default (5%) Constant VOC incidence rate: Voxelotor: [redacted] per year SOC: [redacted] per year
Scenario 4	RETRO voxelotor RTT decrease; [redacted]% relative reduction applied for 2 years		Baseline: [redacted]% Year 1-2: rate of discontinuation [redacted]% Year 3+: rate of discontinuation default (5%)
RTT, regular transfusion therapy; QALYs, quality adjusted life years			

Scenario analysis results are summarised in Table 11.

Table 11 Summary of sensitivity analysis results (discounted, £)

	Difference (voxelotor versus comparator)			
	LY	**QALYs**	**Total cost**	**ICER/QALY**
Scenario 1	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year *Less costly, more effective				

2.2.4. Disaggregated results of the base-case incremental cost-effectiveness analysis

Disaggregated results from the base case cost-effectiveness analysis are presented above (Section 2.2.1). Results by health state are not applicable due to the nature of the discrete event simulation (DES) model. A disaggregated QALY breakdown for SCD-related events is presented in Table 12 and a graph showing the accrual of QALYs over time is presented in Figure 5.

Table 12 Disaggregated QALY breakdown for SCD-related events (base case, not discounted)

	Voxelotor	SOC	Difference
Baseline QALYs (before adjustment)	[redacted]	[redacted]	[redacted]
QALYs after adjust. for SCD, Hb, RTT	[redacted]	[redacted]	[redacted]
Utility adjustments	[redacted]	[redacted]	[redacted]
General sickle cell disease	[redacted]	[redacted]	[redacted]
Hb	[redacted]	[redacted]	[redacted]
RTT	[redacted]	[redacted]	[redacted]
QALY decrements	[redacted]	[redacted]	[redacted]
ARF	[redacted]	[redacted]	[redacted]
Arrythmias	[redacted]	[redacted]	[redacted]
Cardiomegaly	[redacted]	[redacted]	[redacted]
CKD	[redacted]	[redacted]	[redacted]
ESRD	[redacted]	[redacted]	[redacted]
Gallstones	[redacted]	[redacted]	[redacted]
Heart Failure	[redacted]	[redacted]	[redacted]
Leg Ulcer	[redacted]	[redacted]	[redacted]
Osteomyelitis	[redacted]	[redacted]	[redacted]
Osteonecrosis	[redacted]	[redacted]	[redacted]
Pulmonary hypertension	[redacted]	[redacted]	[redacted]
Priapism	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]
VOC	[redacted]	[redacted]	[redacted]
Overall patient QALYs	[redacted]	[redacted]	[redacted]
Mean patient utility			

CKD, chronic kidney disease; ESRD, end-stage renal disease; Hb haemoglobin; QALY, quality adjusted life year; RTT: regular transfusion therapy; SOC, standard of care; VOC, vaso occlusive crisis

Figure 5. Accrual of QALYs over time (cumulative, not discounted)

References

1. Pfizer. A Retrospective Data Collective and Analysis Study of Patients with Sickle Cell Disease (SCD) Who Have Been Treated With Oxbryta (Voxelotor) - Protocol. 2021.
2. Andemariam B, Idowu M, Shah N, et al. 5559749 A Multicenter, Retrospective Study on Real-World Experience Of Patients With Sickle Cell Disease Treated With Voxelotor. HemaSphere. 2023;7(S1).

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	AOFAC Foundation

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	None Applicable
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None Applicable
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that not all relevant evidence has been taken into account in term of patient non participation during appraisal process
2	No. We are concerned that NICE does not believe Voxeletor represents value for money the NHS and the taxpayer

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

3	No. We are not sure if the provisional recommendation sounds and suitable basis for guidance to the NHS
4	Yes. The preliminary recommendation will have a direct impact on patients with Sickle Cell Disorder (SDC); SCD affects mostly people of Black Minority Ethnic group race; What is more, there is limited to new safe and effective treatment for SCD
5	Yes. It will have adverse effect on patients with SCD
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

National Haemoglobinopathy Panel
gst-tr.haemoglobinpanel@nhs.net
https://www.nationalhaempanel-nhs.net
Women's and Children's Academic Health - Kings College London
Becket House, 1 Lambeth Palace Rd
London, SE1 7EU

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NHSE National Haemoglobinopathy Panel (NHP), Haemoglobinopathy Coordinating Centres (HCCs) and Specialist Haemoglobinopathy Teams (SHTs)

National Haemoglobinopathy Panel
https://www.nationalhaempanel-nhs.net

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	None
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None with us an organisation
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..

Please return to: **NICE DOCS**

National Haemoglobinopathy Panel
https://www.nationalhaempanel-nhs.net

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

1	Recommendation 1 and 1.2: We are concerned that this recommendation does not take into account accumulating real world evidence on the use of Voxelotor in clinical practice in patients Sickle Cell Disease, these publications all confirm the findings from the HOPE trial, (Shah N et al (2022), Bade NA et al 2022) all confirm both the haemoglobin rise of greater than 10g/L in two thirds of patients treated with Voxelotor and have additionally shown a decrease in units of blood required where Voxelotor is used in patients on transfusion. While the key trial did not include transfused patients as this could have confounded the primary endpoint, real world data has shown a reduction in transfusions, Shah N et al reported a 52% reduction in mean transfusion rate per patient-year. Sickle cell disease is NOT a priority. It is currently a subject of disparity and inequity in the NHS, globally there is limited option for therapy, it is more or less neglected
2	Recommendation 3.3: We are concerned this recommendation does not seem to take account (or recognise) standard clinical practice in the UK, based on the findings from multiple clinical trials including the BABY HUG study, UK guidance and hence standard practice is for ***all*** children with sickle cell disease to be offered Hydroxycarbamide, in adult services similar practice is undertaken with Hydroxycarbamide discussed with all patients and offered any eligible patient, such as a patient with sickle complication such as pain or one who wishes to commence the medication. Hence for us the clinicians managing sickle cell disease patients positioning Voxelotor as second line therapy reflects our standard practice in the UK. Please refer to British Society of Haematology Guidelines on the Use of Hydroxycarbamide in Sickle Cell (QURESHI A et al https://doi.org/10.1111/bjh.15235) Placing Voxelotor as second line therapy simply recognises standard UK practice in our haemoglobinopathy clinics and in line with expert opinion - 1: Lugthart S, Ginete C, Kuona P, Brito M, Inusa BPD. An update review of new therapies in sickle cell disease: the prospects for drug combinations. Expert Opin Pharmacother. 2024 Mar 4:1-14. 2: Inusa BPD, Mnika K, Babiker S. An expert review of voxelotor for the treatment of hemolytic anemia in patients with sickle cell disease: 'bridging the gap between laboratory data and patient related outcomes'. Expert Rev Hematol. 2023 Jul-Dec;16(8):585-591. As noted by the committee nearly two thirds of patients enrolled in the HOPE trial received hydroxycarbamide consistent with the positioning of Voxelotor as second line therapy. Of note while Hydroxycarbamide is widely offered to patients, in practice most paediatric services have between 30-60% of their patient population on this medication regularly and that percentage is lower in adult clinics in the UK (data reported to the SSQD Dashboard) with only 20-40% of eligible adult patients in most services on regular Hydroxycarbamide therapy. There is a large unmet need especially in adults with sickle cell disease for whom Hydroxycarbamide can become ineffective with ageing either due to dose limitations or other intolerances for example with severe renal impairment. As recognised in this recommendation there are patients for whom Hydroxycarbamide is not an acceptable option due to concerns around fertility, cancer risk or a side effect such as hair loss, for proportion of these patients Voxelotor offers a chance as disease amelioration, this cohort of patients are regularly reviewed in and across all our services. Additionally there is also a cohort of patients who are difficult or impossible to transfuse due to alloimmunisation, for whom a drug such as Voxelotor is very impactful, a number of clinicians in our group have patients in their services on Voxelotor from the named and then early access programs offered by the company who derive ongoing benefit.
3	Recommendation 3.5 We are concerned about the haemoglobin thresholds discussed here, as it does not note the added impact of organ damage, a haemoglobin of 70g/l in a well 20year old with

Please return to: **NICE DOCS**

National Haemoglobinopathy Panel
https://www.nationalhaempanel-nhs.net

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

	sickle cell disease may not require any intervention however a similar haemoglobin level in the same patient 10 years later with added comorbidities including cardiac impairment would most likely require intervention. It is essential to note the level of Haemoglobin taken out of the context of a patient's clinical situation can be poorly understood. In clinical practice Voxelotor would be offered to patients across a range of haemoglobin thresholds taking other clinical factors into account.
4	Recommendation 3.6 We agree with the patient and clinical experts on the impact of an improved haemoglobin level on sickle cell disease patients.
5	Recommendation 3.7 We are concerned this recommendation does not seem to recognise the overwhelming and urgent unmet need for treatments individuals with Sickle cell disease that exists now. Voxelotor by improving haemoglobin levels offers an immediate benefit to patients that is reported to be of value to patients (as noted by the patient and clinical expert on the panel). Longer term impacts of the therapy on organ function can be collected with the treatment in use the clinic and following up the real world data studies.
6	Recommendation 3.12-13 It is worth noting haemoglobin both reduces with age and accruing comorbidities in adults with Sickle cell disease, there is good evidence of the effect of anaemia on cardiac function and one of the standard interventions that clinician put in place for evolving organ impairment aims to improve haemoglobin and reduce the sickle proportion of their blood. Certain patients with sickle cell disease who have absolutely no options to be treated, **are left with zero options** and the decision made for them to have increased morbidity and die much earlier than even the average life expectancy of a sickle cell patient in the UK
7	3.14 We agree with the patient and clinical experts and the company about the utility of EQ-5D health related instrument. Although frequently for health economic assessment EQ-5D is a tool that is inadequate at assessing the quality of life of patients with sickle cell disease, a chronic lifelong condition. Individuals with Sickle cell disease have a symptom burden which will be impacted by anaemia, they manage multiple hospital appointments, as well as competing comorbidities, patients also manage a high burden of fatigue, significant chronic pain burden, and a well-recognised mental health burden with anxiety and depression.
8	2.22 - The leaders and clinicians within haemoglobinopathies network and families are keen to see the Voxelotor remains and option for treatment www.antionalhaempanel-nhs.uk

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the

Please return to: **NICE DOCS**

National Haemoglobinopathy Panel
https://www.nationalhaempanel-nhs.net

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

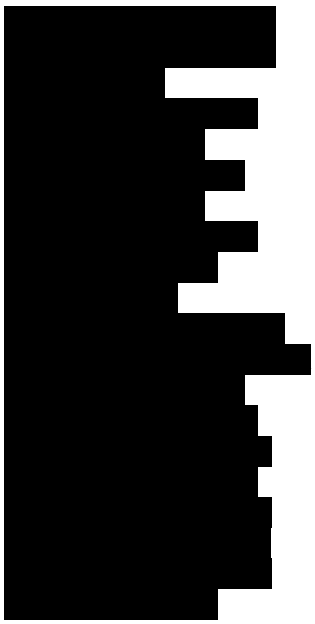
following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Signed on behalf of the National Haemoglobinopathy Panel (NHP) and Haemoglobinopathies Coordinating Centres (HCCs) by:



Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UK Forum on Haemoglobin Disorders

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Global Blood Therapeutics who formerly owned Voxelotor have provided an unrestricted educational grant to support the UK forum's educational meetings in 2023. This funding is applied for by the forum and provided by a number of pharmaceutical companies including Global Blood Therapeutics, without restriction, to support educational events aimed at its membership and affiliates. The funding provided is in no way related to the any products mentioned in the stakeholder list.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none
Name of commentator person completing form:	[redacted] – [redacted] UK Forum on Haemoglobin disorders

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Recommendation 1 and 1.2: We are concerned that this recommendation does not take into account accumulating real world evidence on the use of Voxelotor in clinical practice in patients Sickle Cell Disease(SCD), these publications all confirm the findings from the HOPE trial, (Shah N et al (2022), Bade NA et al 2022) all confirm both the haemoglobin rise of greater than 10g/L in

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

	two thirds of patients treated with Voxelotor and have additionally shown a decrease in units of blood required where Voxelotor is used in patients on transfusion. While the key trial did not include transfused patients, real world data has shown a reduction in transfusions, Shah N et al reported a 52% reduction in mean transfusion rate per patient-year.
2	Recommendation 3.3: We are concerned this recommendation does not seem to take account (or recognise) standard clinical practice in the UK, based on the findings from many trials including the BABY HUG study, UK guidance and hence standard practice is for ***all*** children with SCD to be offered Hydroxycarbamide, in adult services similar practice is undertaken with Hydroxycarbamide discussed with all patients and offered any eligible patient, such as a patient with a sickle complication such as pain or one who wishes to commence the medication. Hence for us the clinicians managing SCD patients positioning Voxelotor as second line therapy reflects our standard practice in the UK. Please refer to British Society of Haematology Guidelines on the Use of Hydroxycarbamide in Sickle Cell (Qureshi A et al https://doi.org/10.1111/bjh.15235) Placing Voxelotor as second line therapy simply recognises standard UK practice in our haemoglobinopathy clinics. Of note while Hydroxycarbamide is widely offered to patients, in practice most paediatric services have between 30-60% of their patient population on this medication regularly and that percentage is lower in adult clinics in the UK (data reported to the SSQD Dashboard) with only 20-40% of eligible adult patients in most services on regular Hydroxycarbamide therapy. There is a large unmet need especially in adults with SCD for whom Hydroxycarbamide can become ineffective with ageing either due to dose limitations or other intolerances for example with severe renal impairment. As recognised in this recommendation there are patients for whom Hydroxycarbamide is not an acceptable option due to concerns around fertility, cancer risk or a side effect such as hair loss, for proportion of these patients Voxelotor offers a chance as disease amelioration, this cohort of patients are regularly reviewed in and across all our services. Additionally there is also a small cohort of patients who are difficult to transfuse due to alloimmunisation, for whom a drug such as Voxelotor is very impactful, a number of clinicians in our group have patients in their services on Voxelotor from the named and then early access programs offered by the company who derive ongoing benefit.
3	Recommendation 3.5 We are concerned about the haemoglobin thresholds discussed here, as it does not note the added impact of organ damage, a haemoglobin of 70g/l in a well 20year old with SCD may not require any intervention however a similar haemoglobin level in the same patient 10 years later with added comorbidities including cardiac impairment would most likely require intervention. It is essential to note the level of Hb taken out of the context of a patient's clinical situation can be poorly understood. In clinical practice Voxelotor would be offered to patients across a range of haemoglobin thresholds taking other clinical factors into account.
4	Recommendation 3.6 We agree with the patient and clinical experts on the impact of an improved Haemoglobin level on SCD patients.
5	Recommendation 3.7 We are concerned this recommendation does not seem to recognise the overwhelming and urgent unmet need for treatments individuals with SCD that exists now. Voxelotor by improving haemoglobin levels offers an immediate benefit to patients that is reported to be of value to patients (as noted by the patient and clinical expert on the panel). Longer term impacts of the therapy on organ function can be collected with the treatment in use the clinic and following up the real world data studies. It is important that the committee take on board the reducing utility of hydroxycarbamide in the ageing and older patient with SCD, it also has limitations in in patients with intractable leg ulceration on Hydroxycarbamide.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

	Transfusion is also limited for a cohort of patients which includes even paediatric age patients with rare allo-imunisation, or who refuse blood on religious grounds.
6	Recommendation 3.12-13 It is worth noting haemoglobin both reduces with age and accruing comorbidities in adults with SCD, there is good evidence of the effect of anaemia on cardiac function and one of the standard interventions that clinicians put in place for evolving organ impairment aims to improve haemoglobin and reduce the sickle proportion of their blood. There is also a cohort of patients who do not have transfusion as an option due to alloimmunisation, risk of delayed haemolytic transfusion reactions and rare blood type. We currently manage these patients with erythropoietin support which unfortunately can result in increased pain episodes but at present there would be no other option for these patients. Voxelotor would have a significant role in this group of patients – as they are rarely transfused their outcomes are not as easily measured but they should be taken into consideration when discussing transfusion reduction. Please also note point 6 above.
7	3.14 -The forum agrees with the patient and clinical experts and the company about the utility of EQ-5D health related instrument. Although frequently for health economic assessment EQ-5D is a tool that is inadequate at assessing the quality of life of patients with SCD, a chronic life long condition. Individuals with SCD have a symptom burden which will be impacted by anaemia, they manage multiple hospital appointments, as well as competing comorbidities, patients also manage a high burden of fatigue, significant chronic pain burden, and a well recognised mental health burden with anxiety and depression.
8	2.22 - The clinicians in the UK Forum for haemoglobin disorders would welcome Voxelotor via a managed access program

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Sickle Cell Society

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	In the financial year 2023/2024 we received a total of £110K from Pfizer. £80K was via a national grant process and the remaining £30K were small grants to support specific patient/families services. The £30K will cease at the end of the financial year ending 31 March 2024. The £80K is non-recurrent and is to pump-prime specific work with the NHS in the North West of England. This is unlikely to start until June 2024.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable[Insert disclosure here]
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We apologise for the slight delay in submitting our response, due to the capacity challenges of a charity of our size.
2	This is the fourth appraisal of Voxelotor. We are concerned that even at this stage, not all of the relevant evidence has been taken into account. We therefore would like to reiterate our previous

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

	written submissions to NICE for this appraisal. We have looked carefully as to why the NICE appraisal committee made their recommendation, having met in private. We are where we are, but we believe that meeting should have included patient and clinical experts to help address any evidence uncertainties.
3	It is accepted by NICE that Voxelotor has the potential to address health inequalities associated with sickle cell disorder (SCD) and the unmet need for new safe and effective SCD treatments. We are not convinced from a patient advocacy perspective that the summaries of clinical effectiveness are a reasonable interpretation of evidence. Regarding the point that the key trial was short, we provided evidence from our patient experts who were involved with the trial. They have clearly set out the benefits to their quality of life as a result of receiving Voxelotor. The use of the term long term benefits is relative. This is because Voxelotor has and continues to be available for SCD patients in the USA for some time. We do not have up to date data from USA studies, but believe that the company can provide further data on benefits for SCD patients from those studies.
4	Regarding whether the NICE recommendations are sound and a suitable basis for guidance to the NHS. The UK's SCD population is at least equivalent to France and it is growing. Denying access to patients because of uncertainties about cost effectiveness estimates and acceptable use of NHS resources is in our view flawed. This is because there has been so little innovation in SCD for decades that comprehensive cost effectiveness data is lacking and neither fits neatly into the NICE models. The fact that Voxelotor is available in Europe and the USA , should not be simply dismissed by NICE as not relevant because you have different responsibilities than the FDA or EMA and that your processes are recognised worldwide. That may be so, but if SCD patients do not have access to Voxelotor in the UK but friends and family in other countries do, it remains a puzzling conundrum for the SCD community in the UK. The reality is that all new SCD modifying treatments are going to be more expensive that the two standard treatments currently available. If NICE looks at the bigger picture of unmet needs for the SCD community it has to accept that with the revocation of the licence by the MHRA for Crizanlizumab, we are going backwards in that the two standard SCD treatments remain the only treatments available. We emphasise this point because it goes to the question of whether there are any aspects of the recommendation that need particular consideration to ensure NICE avoids unlawful discrimination against any group. In our view the effect of the recommendation is that it widens health inequalities and unmet need for the SCD community who whilst not exclusively, are mainly people from black heritage.
5	NICE will know from our previous written appraisal submissions, that we were clear from the outset that Voxelotor could have been assessed for use with a managed access agreement if the company had put forward a managed access proposal to NICE. Whilst that is a matter for the company, we were pleased to know from the Voxelotor appeal hearin, that this was something the company was considering. We remain of the view that taking time to address any uncertainties through a managed access route is therefore a measured and wise way forward and of course enable access to patients. If the company do decide to put forward a managed access proposal, we urge that clinical and patient experts are part of the process to ensure that any data asks are proportionate and reasonable for the system , having regard to our earlier point about the paucity of data for new SCD treatments.
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

Single Technology Appraisal

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

I am a clinical psychologist working in a specialist haemoglobinopathy treatment center. I work with patients with sickle cell disease to help manage symptoms, address social and occupational challenges related to having a life-long condition, reduce reliance on opioid pain-relievers, and manage relationships with healthcare staff.
I have patients who tell me they had a good result from taking voxelotor. They report less fatigue and fewer crises, and less pain overall. Many of my patients are increasingly dissatisfied with their current treatments and would welcome an alternative.
I appreciate the above testimony is anecdotal, but I include it because in the work that I do having a treatment option that helps even a little allows people to make further changes to benefit their lives, reduce inequality, and reduce need for health and social care resources.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No. Voxelotor does have a role in sickle cell disorders. There needs to be recommendation to support the use of voxelotor and collect further data to analyse. The full potential of the medication on patients have not been proven well.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No
I have a patient who since starting Voxelotor, been able to do more. Voxelotor has improved his fatigue.a He is able to help his wife at home and his 3 children. In his own word, he tells me ' my wife does not nag me anymore ‘He is able to wake up early and do school drop which he was not able to do before starting voxelotor. He applied for PIP due to fatigue and

not being able to work full time. He felt inadequate not being able to look after his family. But he is so much happier in himself. He just has stopped coming to hospital to see me very much and my long consultations in clinic is no longer a routine. He tells me he just needs his monitoring blood test and the medication.
The impact voxelotor on him has not been accurately measured in monetary value. In the longer term he saves NHS services time and money. He will reduce the use of public funds. This medicine is cost effective for . .

There are many others like him in whom I had just not managed to get the medication started. The programme was open for a short period of time.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

These group of patients have been disadvantaged for years from underfunding of services. Therefore their voices may not always be well heard and they may lack confidence to speak up on how the illness impacts them. What I find as a consultant working in an ethnic minority service, advocacy is a role I have had to take on. This is not something I needed to do with cancer services which was my previous role as a haematologist.
I hope all these factors are taken into consideration when NICE is making a recommendation. It is not like for like compared to other chronic disorders.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Example 1

We are concerned that this recommendation may imply that ……..

1

Sickle cell disease is underprioritised, underestimated and neglected

2

Certain patients with sickle cell disease who have absolutely no options to be treated, are left with zero options and the decision made for them to have increased morbidity and die much earlier than even the average life expectancy of a sickle cell patient in the UK

3

Cost-effectiveness of very expensive treatments in those patients with a history of significant transfusion reactions if they do experience complications and need blood transfusions, have not been carefully weighed up against the cost of voxelotor which can in certain situations mitigate this risk.

4

Sickle cell patients will continue feeling let down and discriminated by the lack of funding of drugs such as voxelotor which as good safety profile and has proven in the HOPE trial and in the real word experience to be of benefit in certain patients. Patients will lose the trust in the authorities and will stop participating in clinical trials if those almost always lead to no access to the drugs tested and this will have a big knock off effect on the care delivered to our patients in the UK as well the scientific development in this disease globally.

Has all of the relevant evidence been taken into account?

yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

yes but see my additional comments which imply more detailed emphasis on cost effectiveness in certain sickle cell subgroups should be put

Are the recommendations sound and a suitable basis for guidance to the NHS?

The Voxelotor should be accessible free of charge to certain sickle cell patients who fulfil certain clinical criteria and we have a national SOP for this.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Sickle cell disease has always been under prioritised, under resourced and underfunded compared to all other chronic disorders. In the recent 10 years there has been increasing motivation to develop new treatment but yes these do not make it to the market. This leaves a huge unmet need for these patients for who we only have hydroxyurea and blood transfusions to treat with. The first one does not suit / treat everyone effectively and the latter leads to huge costs. Curative options even more limited and majority of patients not eligible. Hence new drugs with good safety profiles and good

outcomes in international trials such as the voxelotor, should be given access to with careful gatekeeping of the eligibility and prospective data collection something which as NHP can work on in a very scientific approach.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

No
The HOPE trial, (Shah N et al (2022), Bade NA et al 2022) all confirm both a haemoglobin rise of greater than 10g/L in two thirds of patients treated with Voxelotor and additionally showed a decrease in units of blood required where Voxelotor is used in patients on transfusion.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

NO
Although frequently used as a health economic assessment tool, EQ-5D is inadequate at assessing the quality of life of patients with SCD, a chronic lifelong condition. The symptom burden in SCD is impacted by anaemia and multiple co-morbidities. Fatigue is significant, as well as acute and chronic pain.
There is a need for frequent hospital attendance and the QOL is akin to someone on regular dialysis.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations fail to recognise the overwhelming and urgent unmet need for new treatments for individuals with SCD. Voxelotor by improving haemoglobin levels offers an immediate benefit (response within 2 weeks) to patients that is reported to be of value to patients. Response is also sustained as shown in the HOPE study that assessed patients up to 72 weeks.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

YES

This group of patients have faced racial discrimination and disadvantage from the healthcare system and its professionals. This is highlighted in the 'No ones listening report' - 15/11/21, link below, whereby negative attitudes towards sickle cell patients and inadequate investment in sickle cell care where clearly demonstrated.
https://www.sicklecellsociety.org/wp-content/uploads/2021/11/No-Ones-Listening-Final.pdf
This draft guidance appears to reinforce this.

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities.	

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

	Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**	
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Pfizer UK Ltd.	
• Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nothing to disclose.	

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

Name of commentator person completing form:	[redacted]	
Comment number	**Comments**	**EAG response**
1	**Executive summary** The company would like to thank the NICE committee for issuing an updated draft guidance and explicitly expressing their preferred scenario for cost-effectiveness. The company appreciates the steps the committee has made to recognise the historic and ongoing inequalities relating to people with sickle cell disease (SCD), particularly the systemic underfunding of research into SCD. As a result, there is an increased necessity for expert clinical opinion when developing an accurate economic evaluation for treating haemolytic anaemia in people with SCD. The company welcome the committee's decision to align with the company base case for their preferred assumptions relating to, utility benefit, haemoglobin increase after transfusion, time-to-event analysis and the rate of transfusion therapy in the standard of care (SOC) arm. In response to the ACD, the company has attempted to address the following outstanding uncertainties: • <u>Positioning:</u> Providing further comments on the uncertainties highlighted in the draft guidance around second line positioning of voxelotor	No comment

Please return to: **NICE DOCS**

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

	• Regular transfusion therapy with voxelotor: a new observational study (Retrospective Real World Oxbryta Data Collection and Analysis Study [RETRO]) which provides real-world evidence (RWE) demonstrating the impact of voxelotor reducing the rate of regular transfusion therapy (RTT) by [redacted]%. This estimate is also supported by additional evidence from the Symphony Database, a small UK RWE study and three other single centre/case study reports. The result from the RETRO study has been applied in the updated company base-case and informed scenario analyses. • Long-term outcomes related to VOCs and ad hoc transfusions: Post hoc analyses from the HOPE-open label extension (OLE) study identified a statistically significant reduction in the mean number of VOCs per patient per year (PPPY) in the continuing voxelotor group compared with the voxelotor naïve group. This estimate has been explored in scenario analysis to demonstrate the impact of this uncaptured benefit. The HOPE-OLE also demonstrated a reduction in the number of ad hoc transfusions PPPY. The impact in reducing the need for ad hoc transfusions is not captured within the model, however it would likely improve the cost-effectiveness results. In addition to the new evidence and updated base-case, the company has proposed an increased PAS of [redacted]%, corresponding to a net price of £[redacted] per pack representing an additional [redacted]% discount versus the previous PAS submitted. This results in an updated company base-case ICER of £[redacted]. The company has tried to represent a complex disease most accurately with the evidence available, and where possible conducting de novo research to fill evidence gaps. We acknowledge the uncertainties still present in the evidence base and possible decision error associated with	

Please return to: **NICE DOCS**

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

	this complicated disease area. However, we believe that the updated commercial offer and the new ICER range presented based on the latest available evidence, results in a significant improvement in the cost-effectiveness results and represents value for money for the NHS.	
2	**Section 3.3 Population** The company welcomes the committee's decision to appraise voxelotor in line with the company's second line positioning, however, noting that there is still some level of uncertainty remains. In order to address this uncertainty, the company would like to clarify that whilst the terminology second line is not exact and is open for interpretation in the context of SCD, the position has been widely supported by clinical experts. There is an international consensus that all patients with SCD should be offered hydroxycarbamide; this is reflected in numerous guidelines including the British Society of Haematology who recommend hydroxycarbamide for all patients with SCD prior to any other treatment. In addition, hydroxycarbamide is licenced in the UK in SCD patients over 2 years of age 10 whereas voxelotor is indicated in those 12 years and above. It is therefore highly likely that SCD patients presenting with symptoms of the disease in childhood would be offered hydroxycarbamide first since there is no other alternative licenced medicine available. Hydroxycarbamide was available in all countries in the HOPE trial. Two thirds of patients in the HOPE trial were receiving hydroxycarbamide, and it is reasonable to assume that the decision to enrol onto the trial was made because current management of their SCD was not optimal (i.e. an insufficient response to hydroxycarbamide). It is important to note that a stable dose does not equate to stable disease, some patients	One of the key aspects of the positioning of voxelotor is where voxelotor sits in the treatment pathway in relation to patients who require RTT. The HOPE trial excluded patients who received RTT and so the trial provides no information about the proportion of patients who: • were receiving RTT prior to treatment with voxelotor • would have received RTT if they had not started treatment with voxelotor • would not, or no longer, receive RTT due to treatment with voxelotor These issues are central to understanding the cost effectiveness of voxelotor.

	reach the maximum permitted dose of hydroxycarbamide and lose effectiveness. Due to the availability of hydroxycarbamide and its recommendation in treatment guidelines, it is likely that for patients in HOPE who were not taking hydroxycarbamide, it had been either considered and was not suitable or had been used in the past (i.e. patients were ineligible, intolerant, or hydroxycarbamide was insufficiently effective), as it is common practice to only enrol patients who have no licenced alternatives. As noted in paragraph 177 of the Appeal Decision, clinical experts said the proposed position was appropriate in reflecting likely clinical practice.[1] With regards to the suitability of the HOPE trial, the clinical experts also noted that hydroxycarbamide is the standard first-line treatment in NHS practice, and indeed, the high proportion of patients receiving hydroxycarbamide in the HOPE trial was itself an indication that this was not a low risk population. They felt that patients would not have taken part in a trial if their disease had been adequately controlled, and the trial included patients who would otherwise have been eligible for RTT[1]. For these reasons, the company believe the HOPE trial is representative of patients who will use voxelotor in the NHS, of these a proportion will likely receive treatment with RTT to manage their disease in the absence of any alternatives (reflected in the treatment disposition of SOC). The uncertainties around the rate of RTT will be discussed in comment 3. Additionally, as the second draft guidance states, in the model there is a higher proportion of patients on voxelotor monotherapy than observed in the HOPE trial; however, treatment efficacy results have been adjusted to reflect this. It is worth noting that voxelotor demonstrated improvements in haemoglobin response across all subgroups in the HOPE clinical trial, regardless of baseline haemoglobin, hydroxycarbamide use, VOC history, age, sex or race.[2] Furthermore, a	

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

	new observational study [RETRO, (NCT04930328)] provides further evidence on the real-world use of voxelotor. Please see details and results of the study under comment 3 and in Appendix A.	
3	**Section 3.11 Regular transfusion therapy (RTT) with voxelotor** The company accepts that similar patient populations need to be compared between SOC and voxelotor in the model and that the committee's preferred base case assumes [redacted]% of patients would be on RTT on both arms. However, the company do not believe that the proportion of patients on RTT in the voxelotor arm would remain at this level once voxelotor treatment is initiated. In addition to the evidence provided during the previous appraisal, this assumption is now further supported by: • the latest evidence from a new observational study (RETRO), • the updated post-hoc analysis from HOPE open label extension (OLE), • and real-world evidence (RWE) from the UK and single-centre and case studies. In order to receive further confirmation from clinicians on this assumption, Pfizer also conducted a digital advisory board (conducted between 11-18th March, 2024), specifically focusing on the assumptions around the rate of RTT with or without voxelotor. **Retrospective Real World Oxbryta Data Collection and Analysis Study (RETRO, NCT04930328)** RETRO is a post marketing, multicentre, retrospective study of patients ≥ 12 years diagnosed with SCD treated with voxelotor, conducted across nine clinical sites in the US. The results showed a reduction in red blood	All the evidence presented by the company is case series evidence. Most of the evidence is sourced from the US RETRO analysis and from the US Shah study. The other case series evidence presented by the company is of limited value due to low patient numbers. The EAG agrees that the RWE evidence presented by the company demonstrates that patients who were treated with voxelotor experienced a reduction in annual transfusion rates. These data were not comparative; the RWE provides no evidence to show whether any (or all) reductions in transfusion rates can be attributed to treatment with voxelotor. Further, it is not possible to estimate the proportion of patients who were not receiving RTT prior to starting treatment with voxelotor who would have received RTT if they had not been treated with voxelotor using the RWE evidence. The EAG considers that as the impact of voxelotor on the proportion of patients who receive RTT is sourced from the RETRO analysis, RETRO analysis data should also be used to estimate the RTT rate for patients who start treatment with voxelotor ([redacted]%) and to estimate the annual transfusion rate for patients receiving RTT prior to starting treatment with voxelotor ([redacted]). **Impact of voxelotor on RTT** To estimate the impact of voxelotor on the proportion of patients who receive RTT, the company has applied the reduction in the annual transfusion rate experienced by RETRO analysis patients after starting treatment with voxelotor ([redacted]%) to the proportion of patients in the model receiving RTT who are treated with voxelotor ([redacted]%). This reduction is

Please return to: **NICE DOCS**

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

	cell (RBC) transfusions after patients started treatment with voxelotor. Transfusion data was analysed from [redacted] patients, the transfusion rate per-patient-per-year (PPPY) prior to starting voxelotor was [redacted] (SD, [redacted]) compared to [redacted] (SD, [redacted]) in the 1 year following. A subgroup analysis of patients with ≥ 6 transfusions (aligned to the definition of RTT in the model; n = [redacted]), showed that the transfusion rate PPPY decreased from [redacted] (SD, [redacted]) in the year before voxelotor to [redacted] (SD, [redacted]) in the year following. This equates to a reduction of [redacted]% (SD, [redacted]). For more detailed results, please see Addendum. This aligns with the findings of a retrospective analysis of patients ≥ 12 years diagnosed with SCD from the **Symphony Database (Shah et al**.[3]), referenced in B.2.6.9 of the original company submission. Of patients with ≥1 transfusion in the 3 months prior to starting voxelotor (n = 190), the mean annualised transfusion rate decreased from 7.0 (95% CI, 6.4–7.5) to 3.3 (95% CI,2.6–4.1) (-52%,P < 0.001).[3] The RETRO analysis has a couple of key advantages compared with the Symphony database analysis conducted b Shah et al.[3] Firstly, the pre- and post-voxelotor treatment period is longer (12 months vs 3 months) thus helping to reduce the potential regression to the mean effect. The RETRO data is of higher quality because it used a standard electronic data capture (EDC) form similar to clinical trials at all sites. Sites were trained on the data capture. The data also underwent Level 1 and 2 cleaning, which meant any errant data entry or certain missing data was tracked down by data quality.[4] **UK real world evidence (Sanius Health)** Another study monitoring the real-world impacts of voxelotor treatment on RBC transfusion requirements in [redacted] UK patients with SCD who received voxelotor for nearly 18 months (mean ± SD of 526 ± 178 days) found that prior to voxelotor treatment, [redacted] patients had required a RBC transfusion, of which [redacted] required regular transfusions (every < 6	based on the experience of only [redacted] patients who were receiving RTT prior to starting treatment with voxelotor. RTT is a binary variable in the model – either a patient receives RTT with a fixed number of transfusions per year ([redacted]), or they do not. It is inappropriate to apply a reduction in a continuous variable as a reduction to a binary variable. In this case, the approach has overestimated the reduction in the annual transfusion rate for model patients receiving RTT and voxelotor compared to the reduction in the transfusion rate experienced by RETRO analysis patients who received RTT and voxelotor. The reductions in annual transfusion rates for patients who received RTT and voxelotor are: RETRO analysis=[redacted]; model=[redacted]. To equalise the model and RETRO analysis annual transfusion rates, the EAG calculated the correct reduction in the proportion of patients receiving RTT in the voxelotor arm of the model to be [redacted]%. This estimate is based on a starting annual transfusion rate of [redacted] (RETRO analysis) rather than a rate of [redacted] (company model). **<u>Proportion of patients receiving RTT only (model standard of care arm)</u>** In the company model, standard of care arm patients can be divided into the following groups: • Group A: those who were receiving RTT prior to commencing second-line treatment • Group B: those who were not receiving RTT prior to commencing second-line treatment and who would be offered RTT as second-line treatment • Group C: those who were not receiving RTT prior to commencing second-line treatment and who would **not** be offered RTT as second-line treatment The RETRO analysis only provides an estimate of the proportion of patients in Group A ([redacted]%). Without an estimate for Group B, [redacted]% may

	weeks). Following voxelotor initiation, only [redacted] patient required any form of transfusion.[5] **Single centre and case studies** The evidence from these studies, is supplemented by a number of single centre and case studies, reporting the experiences of 24 patients treated with voxelotor, in the US and Qatar (a single case study).[6-9] One study including seven patients reported transfusions decreased by 60% in the 24 weeks following voxelotor initiation.[9] Another reported among the 13 patients treated with voxelotor nine required fewer RBC units, falling from 16.6 RBC units in the prior to treatment with voxelotor to 9.6 RBC units in the year during treatment.[7] A third concluded in patients with SCD who receive frequent simple or exchange blood transfusions for indications other than stroke prevention, tapering the amount of blood administered is possible, and should be considered when these patients are treated with voxelotor.[8] **Clinical Expert advice** The assumption that the rate of RTT with voxelotor is equal to the rate with SOC does not reflect the advice provided by the clinical experts consulted by NICE during and beyond the appraisal committee meetings, who stated in their comments on the draft guidance document *"…most clinicians would not use voxelotor and chronic transfusion as a combination therapy. Voxelotor would be used as an alternative to chronic transfusion"*.[10] Based on this, since voxelotor would be used as an alternative to chronic transfusion and combination therapy is unlikely, it is reasonable to expect fewer RTT in the voxelotor arm of the model. Equally, in the SOC arm, where voxelotor is not available, a proportion of these patients would have to be treated with regular transfusions in the absence of any alternative treatments, resulting in a higher number of regular transfusions in the SOC arm.	be an underestimate of the proportion of patients receiving RTT in the model standard of care arm. The Shah Symphony database analysis (n=3,109) suggests that the proportion of patients that would be in Group A lies between 2% (proportion who had had chelation therapy during the previous 3 months prior to starting treatment with voxelotor) and 6.1% (patients who had received a transfusion during the previous 3 months prior to starting treatment with voxelotor). Therefore, using the RETRO analysis estimate of [redacted]% may overestimate the size of Group A by at least 100% and perhaps by as much as 500%. During the NICE appeal process, NHS clinicians confirmed that the HOPE trial accurately represents the anticipated NHS positioning of voxelotor. HOPE trial CSR data showed that, during the first 72 weeks of the trial, only [redacted] in the placebo arm received ≥6 transfusions (the company definition of RTT is ≥6 transfusions per year). Therefore, HOPE trial evidence suggests that the size of Group B may be very small. As the Shah analysis data suggest that [redacted]% may overestimate the size of Group A by between 100% and 500%, and HOPE trial data suggest the size of Group B may be very small, the EAG considers that using [redacted]% as the proportion of patients in the whole standard of care arm receiving RTT (Group A plus Group B) is likely to be an overestimate rather than an underestimate. **<u>Timing of the impact of voxelotor on RTT</u>** Company scenario 1 results show that the ICER per QALY gained is sensitive to the timing of the reduction in the proportion of patients receiving RTT as a consequence of treatment with voxelotor. In the company base case analysis, it is assumed that the impact of voxelotor on RTT occurs as soon as treatment with voxelotor starts. If there is any delay in the impact of treatment with voxelotor on RTT then the company

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

	This is also supported by The American Society of Hematology Guideline Monitoring Expert Working Group who noted that voxelotor, should be considered to improve the baseline haemoglobin in certain patients to minimise future RBC transfusions[11], effectively naming voxelotor as an alternative to regular transfusions. In order to gather further insights from clinicians on this assumption, Pfizer conducted an advisory board involving [redacted] haematologists who represent the most key treatment centres for SCD, [redacted]haemoglobinopathy coordinating centres (HCC) within England. In this advisory board we asked a poll question; with the routine availability of voxelotor, what impact they believed voxelotor may have on RTT in patients with SCD. There were [redacted] responses: [redacted]([redacted]) believed that voxelotor will decrease RTT in patients with SCD, [redacted]% ([redacted]) believe that voxelotor will have no change on RTT amongst patients with SCD. [redacted] haematologist did not respond.[12] **Conclusion** Based on clinical expert opinion, multiple studies, and published single centre and case studies, the committee's preferred assumption of equal transfusion rates in both treatment arms persisting over the time horizon of the model (lifetime horizon), with equal rates of RTT discontinuation (5% per year) does not reflect clinical practice. In addition, the long-term randomised clinical trial evidence from HOPE-OLE supports that treatment with voxelotor reduces the need for transfusions over time. Please see detailed results under comment 4. Whilst it is difficult to separate regular transfusions from ad hoc RBC transfusions in the literature, the evidence shows that overall transfusion burden reduces with voxelotor and transfusion rates decline more significantly in the subgroup of patients with the highest number of transfusions.	base case ICER per QALY gained would increase. HOPE trial data show that, compared with placebo, treatment with voxelotor had no impact on transfusion rates over the first 72 weeks (albeit in a non-RTT population) and so the true ICER per QALY gained (assuming that everything else in the model is accurate) is likely to lie between the company base case ICER per QALY gained and the company scenario 1 (where it is assumed that it takes 12 months for treatment with voxelotor to have an impact on the proportion of patients receiving RTT) ICER per QALY gained. In summary, the EAG accepts that there is evidence that patients who start treatment with voxelotor experience a reduction in transfusion rates. However, the absence of comparative evidence means that the impact of voxelotor on the proportion of patients receiving RTT is unknown. The impact of voxelotor on the proportion of patients receiving RTT is central to the cost effectiveness of voxelotor. It is, therefore, disappointing that, for a condition that affects 15,000 people in the UK, the company has chosen to use non-comparative evidence from 27 US patients to estimate the impact of voxelotor on the proportion of patients receiving RTT. The EAG has also identified that the cost of ARCET transfusion was substantially lower in the ongoing appraisal of Exagamglogene autotemcel for treating sickle cell disease (ID4016), where the cost per ARCET transfusion was £2,700 instead of the £[redacted] in the company base case. As the cost effectiveness results are sensitive to the proportion of patients receiving RTT, results are also sensitive to the cost of ARCET transfusions (95% of transfusions in the model), the EAG has run scenarios using the ID4016 ARCET cost.

Please return to: **NICE DOCS**

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

	Therefore, the committee's current assumption is incorrect, overly conservative and not supported by evidence that RTT rate is similar in both arms. **Updated base-case** Based on the new evidence, we believe there is a clear rationale to support a modified approach to the Committee's preferred assumption of identical rates of RTT in SOC and voxelotor. RETRO has demonstrated that in the year prior to voxelotor initiation, RTT patients had on average [redacted] transfusions per year, which is similar to our model where RTT costings assume [redacted] transfusions per year. However, in the year following voxelotor initiation, RETRO demonstrated that the number of transfusions in this group was reduced by [redacted]%. For simplicity, we have applied this relative reduction in the model by reducing the percentage of patients on RTT in the voxelotor arm to [redacted]% [redacted] from day one. We have explored the impact of this assumption in scenario analysis.	
4	**Section 3.7 Long term complications** The company are pleased that the committee have considered that, as a rare disease with limited evidence available, the level of evidence supporting surrogate endpoints is not as high as in other conditions and is therefore willing to apply more flexibility when estimating the impact of voxelotor on long-term SCD related complications. The committee however note the high levels of uncertainty in this assumption. The company have shared new post-hoc analysis from the HOPE-OLE which supports this assumption. **VOCs**: The HOPE trial was not powered or designed to show differences in VOCs; nearly half (42%) of patients had only one VOC in the year before enrolment, and those with > 10 were excluded. Nonetheless, the	**VOCs** The EAG thanks the company for the updated HOPE trial OLE evidence on the impact of voxelotor on VOCs. The company has (i) updated the method used to incorporate VOCs into the model and (ii) updated the VOC rates in both model treatment arms by replacing HOPE trial data with HOPE-OLE trial data. This new evidence has been included in the model as a scenario (number 2) in which VOCs are modelled using a constant exponential rate that varies depending on whether a patient is treated with voxelotor. This change in approach to modelling VOCs does not address any of the issues discussed during the NICE appeal process, nor does it address the uncertainty around the impact of treatment with voxelotor on long-term SCD complications.

Please return to: **NICE DOCS**

	proportion of patients who experienced a VOC event during the study was numerically lower in the voxelotor 1500 mg group compared to the placebo group (69.3% vs 76.9%). The total number of VOC events was also numerically lower in the voxelotor than in the placebo group (219 vs 293); however, differences were not statistically significant.[2] Post-hoc analysis of the HOPE-OLE data was collected on the number VOCs from the start of the OLE through 28 days after voxelotor discontinuation, similar to RBC transfusions. VOCs were events reported as SCD with crisis or acute chest syndrome. These results demonstrated a reduction in VOCs. A statistically significant reduction of [redacted]% was observed in the mean number of VOCs per patient per year (PPPY in the continuing voxelotor group ([redacted] [SD, [redacted]] vs [redacted] [SD, [redacted]], [redacted]) compared with the voxelotor naïve group. This reduction in VOC events, supports the assumption of long-term benefit associated with continued improvement in haemoglobin levels caused by voxelotor, acting on the underlying molecular basis of SCD. **Ad hoc transfusions:** The HOPE trial did not show a decrease in ad hoc transfusions, however further data on transfusion therapy has been collected from participants in the HOPE open label extension (OLE) for the period from the start of the OLE. Patients who completed the phase 3 HOPE trial (i.e. completed 72 weeks of treatment) were eligible to enrol in the multicentre HOPE Open Label Extension (OLE) study (n = 199). Participants randomised to the placebo (n =62 [34.8%]) or the voxelotor 900 mg arms (n = 58 [32.5%]) of the HOPE trial started once daily voxelotor 1500 mg upon entering the OLE; participants randomised to the 1500 mg arm (n = 58 [32.5%]) of the HOPE trial continued at this dose if they derived clinical benefit and/or until voxelotor was available via an alternative source (commercialisation or a managed access program).	HOPE-OLE study data relate to patients who switched from placebo to voxelotor (and therefore includes the period of time patients were treated with voxelotor). The EAG considers that these data cannot be used to model VOC rates for patients in the model standard of care arm. **<u>Transfusions</u>** RTT transfusion rates, and potentially ad hoc transfusion rates, are the key drivers of the cost effectiveness of voxelotor versus standard of care. It is, therefore, disappointing that transfusion rates are poorly implemented in the company model (RTT is a binary variable and ad hoc transfusions are not modelled). The HOPE trial provides the only comparative transfusion rate evidence for patients treated with/without voxelotor. HOPE trial results (a non-RTT population) suggest that, over 72 weeks, treatment with voxelotor has no impact on the annual transfusion rate. Therefore, inclusion of reduced transfusion rates for patients treated with voxelotor is not supported by the best available evidence. However, the RWE suggests that voxelotor reduces the annual transfusion rate, especially for patients receiving RTT. If future evidence from comparative studies were to reflect RWE data, then a model that included transfusion rates for patients treated with/without voxelotor may allow subgroups for whom treatment with voxelotor is cost effective to be identified. Updated EAG cost effectiveness results are presented at the end of this document (Table 2).

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

	Data were collected on the number of RBC transfusions from the start of OLE through 28 days after voxelotor discontinuation. The mean duration of exposure to voxelotor in the OLE was [redacted] years for those previously treated with placebo in HOPE (voxelotor naïve) and [redacted] years for those continuing voxelotor. The total exposure to voxelotor was [redacted] years for patients continuing on voxelotor 1500mg. The analysis demonstrated a reduction in RBC transfusions. The mean number of transfusions PPPY was lower in the continuing voxelotor group ([redacted] [SD, [redacted]] vs [redacted] [SD, [redacted]], p=[redacted]) compared with the voxelotor naïve group, with the mean number of transfusions per patient [redacted]% lower in the group continuing voxelotor [redacted] vs [redacted]). The results were not statistically significant. For more detailed results, please see Addendum. The reduction in the need for RBC transfusions supports the long-term benefit associated with continued improvement in haemoglobin levels caused by voxelotor. Whilst patients receiving regular scheduled transfusions were excluded from HOPE there was no limit on the number of ad-hoc RBC transfusions that can be given. Ad hoc transfusions still present a considerable burden to the healthcare system; this phase 3 randomised controlled trial evidence demonstrates the long-term reduction in transfusions in patients treated with voxelotor. It is important to note that the impact in reducing the need for ad hoc transfusions is not captured within the model, which would likely improve the cost-effectiveness results.	

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

5	**Company's updated base case** The latest results from the RETRO and HOPE-OLE studies have been incorporated in the updated company model and tested in scenario and sensitivity analyses. The updated company base case includes the following changes to the model: • The rate of RTT in the voxelotor arm is calculated based on RETRO observational study by applying the relative reduction of [redacted]% to the SOC arm, to reflect the results observed in the subgroup of patients with 6 or more RBC transfusion prior to voxelotor. Therefore, RTT on the voxelotor arm equals to [redacted]%. • Reduced net price of £[redacted] per pack. This resulted in a new company base case ICER of £[redacted]/QALY, which is within the range that NICE considers an acceptable use of NHS resources. The following assumptions were tested in scenario analyses: • Applying the data from the HOPE-OLE trial on the reduction on VOCs with voxelotor. In order to do this, the model was updated to remove the previous time-to-event equation for incidence of VOCs; in its place a constant incidence rate of [redacted] VOCs per year for voxelotor and [redacted] VOCs per year for SoC was used in an exponential time-to-event equation with no covariates. • The rate of RTT in the voxelotor arm was calculated based on RETRO observational study by assuming a delayed treatment effect. In order to apply this scenario, rates of RTT on both arms starts with [redacted]% of patients receiving RTT and the relative reduction in RTT of [redacted]% was applied after 1 year on the voxelotor arm. A switch was programmed into the model such that at the end of year one [redacted]% of patients have discontinued RTT on a one-off basis. The company considers this scenario to be overly conservative and not in line with clinical evidence as the RETRO data and other evidence shows immediate treatment effect in the 1st year after introduction of voxelotor. The company considers the new base case to be conservative as there are significant benefits that are not captured in this scenario. For simplicity, VOC incidence rates from HOPE-OLE were not incorporated in the new base case; however they represent a significant uncaptured benefit.

Please return to: **NICE DOCS**

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

Another area of uncaptured benefit is the reduction in ad-hoc transfusions from the HOPE-OLE trial, which is not captured in the cost-effectiveness results as it would have required significant changes to the model, which was not feasible during the timeframe of this consultation.

Further details of the preferred base case, scenario analyses and granular cost-effectiveness outcomes are provided in Addendum.

Table 1. Summary of model changes

Model change	Description	Assumption	ICER (cost/QALY)
-	Committee's preferred assumptions	-	[redacted]
New price	Committee's preferred assumptions + new PAS		[redacted]
Company's new base case	Rate of RTT in the voxelotor arm based on RETRO observational study. Relative reduction of RTT by [redacted]% at baseline	RTT in voxelotor baseline: [redacted]%	[redacted]
Scenario 1	Hypothetical scenario to test the sensitivity of the ICER to different assumptions around RTT displacement with voxelotor. Rate of RTT in the voxelotor arm based on RETRO observational study, assuming a delayed treatment effect; with both arms starting with [redacted]% of patients receiving RTT and applying the relative reduction in RTT of [redacted]% after 1 year.	RTT in voxelotor baseline: [redacted]% RTT in voxelotor year 1: rate of discontinuation [redacted]% RTT in voxelotor year 2+: rate of discontinuation default (5%)	[redacted]

Please return to: **NICE DOCS**

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

Scenario 2	New base case + VOC incidence using results from the HOPE-OLE trial	RTT in voxelotor baseline: [redacted]% Constant VOC incidence rate: Voxelotor: [redacted] per year SOC: [redacted] per year	[redacted]	
Scenario 3	Scenario 1 + time-to-event equations populated with the VOC incidence from HOPE-OLE	RTT in voxelotor baseline: [redacted]% RTT in voxelotor year 1: rate of discontinuation [redacted]% RTT in voxelotor year 2+: rate of discontinuation default (5%) Constant VOC incidence rate: Voxelotor: [redacted] per year SOC: [redacted] per year	[redacted]	
Scenario 4	Hypothetical scenario to test the sensitivity of the ICER on different assumptions around RTT displacement with voxelotor. Testing the sensitivity of the ICER on continued reduction in RTT beyond 1 year after initiation of voxelotor.	Baseline: [redacted]% Year 1: rate of discontinuation [redacted]% Year 2: rate of discontinuation [redacted]% Year 3+: rate of discontinuation default (5%)	[redacted]	
OLE: open-label extension; RTT: regular transfusion therapy; SOC: standard of care; VOC: vaso-occlusive crisis				

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is [redacted] and information that is [redacted]. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

References

1. National Institute for Health and Clinical Excellence. Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403] Appeal. 2023. Available from: https://www.nice.org.uk/guidance/gid-ta10505/documents/html-content-11.
2. European Medicines Agency. Oxbryta: EPAR - Public Assessment Report. 2022. Available from: https://www.ema.europa.eu/en/documents/assessment-report/oxbryta-epar-public-assessment-report_en.pdf [accessed March 2022].
3. Shah N, Lipato T, Alvarez O, et al. Real-world effectiveness of voxelotor for treating sickle cell disease in the US: a large claims data analysis. Expert Review of Hematology. 2022;15(2):167-73.
4. Pfizer. A Retrospective Data Collective and Analysis Study of Patients with Sickle Cell Disease (SCD) Who Have Been Treated With Oxbryta (Voxelotor) - Protocol. 2021.
5. Sanius Health. Monitoring the Real-World Impacts of Voxelotor Treatment on Blood Transfusion Requirements, Quality of Life, and Physiological Wearable Metrics in UK Patients with Sickle Cell Disease. (Pfizer Data on File). 2023.
6. Alshurafa A, Yassin MA. Case report: Safety and efficacy of voxelotor in a patient with sickle cell disease and stage IV chronic kidney disease. Frontiers in Medicine. 2022;9.
7. Bade NA, Giri U, Wang H, Ershler WB. Reduced red cell transfusions and hospitalizations in sickle cell patients treated with voxelotor—Experience from a single center. Transfusion. 2022;62(7):1462-4.
8. Baruwa Etti A, Jones S, Andemariam B. 5610357: Reduction in Blood Transfusion Burden Following Initiation of Voxelotor or Crizanlizumab: A Case Series. HemaSphere. 2023;7(S1).
9. Blyden G, Bridges KR, Bronte L. Case series of patients with severe sickle cell disease treated with voxelotor (GBT440) by compassionate access. American Journal of Hematology. 2018;93(8):E188-E90.
10. National Institute for Health and Clinical Excellence. Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403] Committee Papers. 2023. Available from: https://www.nice.org.uk/guidance/gid-ta10505/documents/committee-papers-2.
11. Chou ST, Hendrickson JE, Fasano RM. Transfusion therapy for sickle cell disease: what's new? Blood Advances. 2023;7(11):2551-3.
12. Pfizer. Asynchronous digital advisory board. Data on file. 2024.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

Table 2 Updated EAG cost effectiveness results

EAG revision	Voxelotor		Standard of care		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Difference versus company base case
A1. New company base case: • patients treated with standard of care who receive RTT=[redacted]% • patients treated with voxelotor who receive RTT voxelotor =[redacted]% • annual transfusion rate for patients who receive RTT=[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
A2. EAG base case: • patients treated with standard of care who receive RTT=[redacted]% • patients treated with voxelotor who receive RTT voxelotor=[redacted]% • annual transfusion rate for patients who receive RTT=[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: EAG base case plus the assumption that the impact of voxelotor on the proportion of patents who receive RTT occurs at 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: New company base case using ID4016 ARCET transfusion cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: EAG base case using ID4016 ARCET transfusion cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; RTT=regular transfusion therapy

Please return to: **NICE DOCS**